# Timetable

## Thursday, October 30, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>18:00-19:05</td>
<td>Opening Session</td>
</tr>
<tr>
<td>19:15-20:30</td>
<td>Networking Reception</td>
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## Friday, October 31, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Hall A</th>
<th>Hall B</th>
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<tbody>
<tr>
<td>08:30-10:30</td>
<td>Plenary Session I: Screening for thrombophilia and pregnancy complications</td>
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<tr>
<td>10:30-11:00</td>
<td>Coffee break and poster viewing</td>
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<tr>
<td>11:00-13:00</td>
<td>Parallel Session II: Heparin, warfarin and novel anticoagulants</td>
<td>Parallel Session III: Epidemiology and risk factors of venous thrombosis in children</td>
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<tr>
<td>13:00-14:00</td>
<td>Lunch break and poster viewing</td>
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<tr>
<td>14:00-16:00</td>
<td>Plenary Session IV: Hemophilia care: Current guidelines and applications of new factor concentrates</td>
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<tr>
<td>16:00-16:30</td>
<td>Coffee break and poster viewing</td>
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<tr>
<td>16:30-18:30</td>
<td>Parallel Session V: Antiplatelet therapy and monitoring</td>
<td>Parallel Session VI: Replacement therapy before surgery of FVII &amp; FXI deficient patients</td>
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## Saturday, November 1, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Hall A</th>
<th>Hall B</th>
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<tbody>
<tr>
<td>08:30-10:00</td>
<td>Industry Symposium</td>
<td>Symposium not included in main CME/CPD credit program For more information see back of Program Book</td>
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<tr>
<td>10:00-10:30</td>
<td>Coffee break and poster viewing</td>
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<tr>
<td>10:30-12:30</td>
<td>Parallel Session VII: Pharmacogenomics; Thrombolytic therapy</td>
<td>Parallel Session VIII: Heparins, warfarin and new anticoagulants for pediatric venous thrombosis</td>
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<tr>
<td>12:30-13:30</td>
<td>Lunch break and poster viewing</td>
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<tr>
<td>13:30-15:30</td>
<td>Plenary Session IX: Immune thrombocytopenia; Bleeding complications of new oral anticoagulants</td>
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<tr>
<td>15:30-16:00</td>
<td>Coffee break and poster viewing</td>
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<tr>
<td>16:00-18:00</td>
<td>Parallel Session X: Primary prevention of venous thrombosis and coronary artery disease</td>
<td>Parallel Session XI: Plasma derived versus recombinant factor VIII concentrates</td>
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Industry ........................................................ 71
Welcome letter

Dear Colleagues,

We would like to personally welcome you to the Congress on Controversies in Thrombosis and Hemostasis (CiTH) in Berlin, Germany.

CiTH is a concept congress dealing mainly with controversial issues in the format of debates and discussions allowing ample time for speaker-participant interaction. Congresses are becoming more and more specialized and monothematic, allowing limited time to fully discuss clinical meaning and the line between Evidence Based Medicine (EBM) and working theories or ideas that are premature to implement into practice. CiTH addresses this need by facilitating effective debate on unresolved clinical and therapeutic dilemmas, supported by expert opinions resulting in agreement on timely issues.

The ability to discuss controversial topics with emphasis on clinical solutions in cases where no agreed-upon answers exist provides clinicians with an insight and a take-home message that ameliorates treatment in the most difficult situations.

We thank you for joining us in shaping and bringing to light a provocative program, and to contributing to a successful and invigorating congress. It is our pleasure and honor to welcome you in Berlin.

Sincerely,

David Varon  
Pier M. Mannucci  
Gili Kenet  

Chairpersons
EXCEMED - Excellence in Medical Education (www.excemed.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net.

EXCEMED-Excellence in Medical Education (www.excemed.org) has submitted the main congress program of the Congress on Controversies in Thrombosis and Hemostasis (CiTH), Berlin, Germany, October 30-November 1, 2014, for accreditation by the European Accreditation Council for Continuing Medical Education (EACCME). There is an official agreement for mutual recognition of CME credits between the European Accreditation Council for Continuing Medical Education (EACCME) and the American Medical Association (AMA).

Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity. The EACCME credit system is based on 1 ECMEC per hour with a maximum of 3 ECMECs for half a day and 6 ECMECs for a full-day event.

The CME accreditation is valid for the main congress program only and does not cover the company-sponsored symposia.

To receive your CME credits, please complete the questionnaire which will be online at http://cith2014.excemed.org and after the Congress on the Congress website. After completing the questionnaire, you will receive your certificate directly from EXCEMED. The link will be open for 3 weeks only.

Italian ECM accreditation:
EXCEMED - Excellence in Medical Education (www.excemed.org) has submitted, in compliance with the procedures indicated by the Italian Ministry of Health, the main congress program of this event n. 1841-69707 Ed. 1, entitled Congress on Controversies in Thrombosis and Hemostasis (CiTH), Berlin, Germany, October 30 – November 1, 2014 to the Italian National Commission for Continuing Medical Education.

ISO 9001 Certification:
EXCEMED has received the ISO 9001 Certification of Quality Management Systems. This Quality certification requires all participants to fill in a scientific questionnaire and to evaluate the overall quality of the event.
General Information

Congress Venue
Maritim proArte Hotel
Friedrichstraße 151
10117 Berlin, Germany

Language
The official language of the Congress is English.

Registration Desk
The registration desk will be open during the following hours:
Thursday, October 30, 2014 15:00 - 20:00
Friday, October 31, 2014 07:30 - 18:00
Saturday, November 1, 2014 08:00 - 18:00

Congress Kit and Name Badge
On arrival at the registration desk you will receive your name badge. Please wear the name badge to all sessions and events.

Certificate of Attendance (non CME/CPD)
You may collect your Certificate of Attendance at the Registration Desk on Saturday, November 1. CME/CPD certificates will be sent electronically after the congress by filling out an online educational evaluation form.

Refreshments
A Networking Reception will be held on Thursday, October 30 at 19:15 in the exhibition area.
Coffee and lunch will be served for participants in the exhibition area during coffee and lunch breaks on Friday, October 31 and Saturday, November 1. Entrance will be with name badges only.

Exhibition
An exhibition will be held concurrently with the congress. Exhibition opening hours are:
Thursday, October 30, 2014 18:00-20:30
Friday, October 31, 2014 08:30-18:00
Saturday, November 1, 2014 08:30-18:00

Poster Display
Please check the Scientific Program for the board number on which you should display your poster(s). Posters should be mounted between 07:30-08:30 on Friday, October 31 and removed by the end of the sessions on Saturday, November 1. Poster presenters should plan to be next to their poster board during coffee breaks.
Dismantling of posters is the responsibility of the presenter. The Organizing Committee is not responsible for posters that are not removed on time.

Safety and Security
Please do not leave any bags or suitcases unattended at any time, whether inside or outside session halls.

Liability
The Congress Secretariat and Organizers cannot accept liability for personal accidents or loss or damage to private property of participants either during or directly arising from the Congress on Controversies in Thrombosis and Hemostasis (CiTH). Participants should make their own arrangements with respect to health and travel insurance.
Congress on Controversies in Thrombosis & Hemostasis

Scientific Program
Thursday, October 30, 2014

18:00-19:05 OPENING SESSION

18:00-18:10 Welcome message by Congress chairpersons
D. Varon, Israel
P.M. Mannucci, Italy
G. Kenet, Israel

18:10-18:20 Award Ceremony
Two Best Abstracts
Young Scientist Award

18:20-19:05 Keynote speaker
What has genetic aetiologic research changed in the clinic of thrombosis and hemostasis?
F.R. Rosendaal, Netherlands

19:15-20:30 NETWORKING RECEPTION
### Friday, October 31, 2014

#### PLENARY SESSION I: SCREENING FOR THROMBOPHILIA AND PREGNANCY COMPLICATIONS

**Chairpersons:** S. Middeldorp, Netherlands  
A. Lubetsky, Israel

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker(s)</th>
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</table>
| 08:30-09:20 | Debate: Screening for thrombophilia | Always: A. Lubetsky, Israel  
Never: I. Martinelli, Italy |
| 09:20-10:10 | Debate: Role of thrombophilia in pregnancy complications | Major: B. Brenner, Israel  
Minor: S. Middeldorp, Netherlands |
| 10:10-10:30 | VEGFA gene promoter polymorphisms and risk of venous thromboembolism in ambulatory cancer patients | P. Ferroni, Italy |
| 10:30-11:00 | Coffee break and poster viewing | |

#### PARALLEL SESSION II: HEPARIN, WARFARIN AND NOVEL ANTICOAGULANTS

**Chairpersons:** I. Birschmann, Germany  
B. Brenner, Israel

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>11:00-11:30</td>
<td>State of Art: NOACs for the treatment and prevention of VTE</td>
<td>A. Lubetsky, Israel</td>
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</tbody>
</table>
| 11:30-12:20 | Debate: NOACs in cardiology | Advantages: E. Lev, Israel  
Limitations: B. Brenner, Israel |
| 12:20-12:40 | Laboratory evaluation of DOAC: Do's and don'ts | I. Birschmann, Germany |
| 12:40-13:00 | Coagulation Resonance Amplitude (CORA) technology provides a novel viscoelastic assessment of simultaneous coagulation component analysis | J. Kashuk, Israel |
| 13:00-14:00 | Lunch break and poster viewing | |

#### PARALLEL SESSION III: EPIDEMIOLOGY AND RISK FACTORS OF VENOUS THROMBOSIS IN CHILDREN

**Chairpersons:** U. Nowak-Göttli, Germany  
H. Van Ommen, Netherlands

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<tbody>
<tr>
<td>11:00-11:20</td>
<td>State of Art: Epidemiology and risk factors of venous thromboembolism in children</td>
<td>H. Van Ommen, Netherlands</td>
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</tbody>
</table>
| 11:20-12:05 | Debate: Should infants with perinatal thrombosis be screened for thrombophilia and treated by anticoagulants? | Yes: U. Nowak-Göttli, Germany  
No: S. Revel-Vilk, Israel  
Discussion |
12:05-12:50 Debate: Is there a role for primary anticoagulant prophylaxis in children with acute lymphocytic leukemia?
12:05 Yes: U. Nowak-Göttl, Germany
12:25 No: H. Van Ommen, Netherlands
12:45 Discussion

12:50-13:00 Clinical and laboratory characteristics of children with venous thromboembolism and protein C-deficiency: An observational Israeli-German cohort study
V. Limperger, Germany

13:00-14:00 Lunch break and poster viewing

14:00-16:00 PLENARY SESSION IV: HEMOPHILIA CARE: CURRENT GUIDELINES AND APPLICATIONS OF NEW FACTOR CONCENTRATES
Hall A

Chairpersons: E. Santagostino, Italy
K. Fischer, Netherlands

14:00-14:20 State of Art: Hemophilia care: Current guidelines and applications of new factor concentrates
K. Fischer, Netherlands

14:20-15:10 Debate: Prophylaxis for children with hemophilia should start early or after joint bleed? Is low dose regimen preferable to standard dose?
14:20 Early start and frequent dosing: R. Ljung, Sweden
14:40 Lower doses: E. Santagostino, Italy
15:00 Discussion

15:10-16:00 Debate: Should we screen children for coagulopathies prior to surgery?
15:10 No - not always: C. Bidlingmaier, Germany
15:30 Yes - most of the time: S. Revel-Vilk, Israel
15:50 Discussion

16:00-16:30 Coffee break and poster viewing

16:30-18:30 PARALLEL SESSION V: ANTIPLATELET THERAPY AND MONITORING
Hall A

Chairpersons: A. Michelson, USA
M. Cattaneo, Italy

16:30-17:20 Debate: Monitoring anti platelet therapy
16:30 Helpful: R. Storey, UK
16:50 Not helpful: M. Cattaneo, Italy
17:10 Discussion

17:20-18:10 Debate: New antiplatelet agents
17:20 Advantages: E. Lev, Israel
17:40 Limitations: A. Michelson, USA
18:00 Discussion

18:10-18:20 Amyloid peptide-dependent activation of human platelets: Essential role for Ca2+ and ADP
G. Pula, UK

18:20-18:30 The novel NOX inhibitor 2-acetylphenothiazine impairs collagen-dependent thrombus formation in a GPVI-dependent manner
G. Pula, UK
Friday, October 31, 2014

16:30-18:30 PARALLEL SESSION VI: REPLACEMENT THERAPY BEFORE SURGERY OF FVII & FXI DEFICIENT PATIENTS

Chairpersons: P.M. Mannucci, Italy  
B. Brenner, Israel

16:30-17:20 Debate: Replacement therapy before surgery of FVII & FXI deficient patients
16:30 Yes: P. Bolton-Maggs, UK
16:50 Low dose of rFVIIa for both: O. Salomon, Israel
17:10 Discussion

17:20-18:10 Debate: Prevention and treatment of bleeding in liver disease: Should hemostatic agents be used?
17:20 Yes: T. Lisman, Netherlands
17:40 No: P.M. Mannucci, Italy
18:00 Discussion

18:10-18:30 Thrombin generation and bleeding phenotype in patients with mild hemophilia A with discrepant FVIII assays
E. Santagostino, Italy
Saturday, November 1, 2014

08:30-10:00 Industry Symposium:

Supported session. Not included in the CME/CPD credit program. For program details please refer to page 75 of the Industry Section at the back of the Program Book.

10:00-10:30 Coffee break and poster viewing

10:30-12:30 PARALLEL SESSION VII: PHARMACOGENOMICS; THROMBOLYTIC THERAPY

Chairpersons: D. Varon, Israel
Y. Caraco, Israel

10:30-11:10 State of Art: Pharmacogenomics in thrombosis and hemostasis
Y. Caraco, Israel

11:10-11:50 State of Art: Catheter guided thrombolysis in VTE
A.I. Bloom, Israel

11:50-12:10 Extracellular fibrinogen binding protein inhibits thrombus formation by interacting with platelets in a fibrinogen-dependent manner: Unexpected results and novel hypotheses
G. Pula, UK

12:10-12:30 Catheter directed thrombolysis along with mechanical thromboaspiration in the management of proximal lower limb deep venous thrombosis: A prospective study with 6-month follow-up
S. Patra, India

12:30-13:30 Lunch break and poster viewing

10:30-12:30 PARALLEL SESSION VIII: HEPARINS, WARFARIN AND NEW ANTICOAGULANTS FOR PEDIATRIC VENOUS THROMBOSIS

Chairpersons: C. Bidlingmaier, Germany
I. Martinelli, Italy

10:30-10:50 State of Art: Heparins and warfarin for pediatric venous thrombosis: Current recommendations
C. Bidlingmaier, Germany

10:50-11:35 Debate: New oral anticoagulants in children: Should they be prescribed for special (off label) situations?

10:50 Yes: I. Martinelli, Italy
11:10 No: A. Michelson, USA
11:30 Discussion

11:35-12:20 Debate: Antiphospholipid syndrome in children: Should similar diagnostic criteria be applied?

11:35 Yes: V. Pengo, Italy
11:55 No: T. Strauss, Israel
12:15 Discussion

12:20-12:30 Is inherited thrombophilia testing justified in children with perinatal arterial ischemic stroke?
D. Coen Herak, Croatia

12:30-13:30 Lunch break and poster viewing
**PLENARY SESSION IX: IMMUNE THROMBOCYTOPENIA; BLEEDING COMPLICATIONS OF NEW ORAL ANTICOAGULANTS**

**Chairpersons:**
- F. Peyvandi, Italy
- D. Varon, Israel

**13:30-14:30 Debate:** The role of thrombopoietics in ITP

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<tr>
<th>Time</th>
<th>Panelist</th>
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<tr>
<td>13:30</td>
<td>1st line: J. Bussel, USA</td>
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<tr>
<td>13:50</td>
<td>3rd line: M. Cattaneo, Italy</td>
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**14:30-15:10 State of Art:** Bleeding associated with new oral anticoagulants: Assessing the risk and management

- D. Varon, Israel

**15:10-15:30 Strategic management plan to successfully implement New Oral Anticoagulants (NOAs) in anticoagulated patients 2010-2014**

- A. González Argüello, Spain

**16:00-17:45 PARALLEL SESSION X: PRIMARY PREVENTION OF VENOUS THROMBOSIS AND CORONARY ARTERY DISEASE**

**Chairpersons:**
- C. Patrono, Italy
- Y. Caraco, Israel

**16:00-16:40 State of Art:** Extended venous thromboembolism prophylaxis in medically ill patients

- Y. Caraco, Israel

**16:40-17:45 Debate:** Primary prevention of coronary artery disease by aspirin

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<th>Time</th>
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<tr>
<td>16:40</td>
<td>No: R. Storey, UK</td>
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<td>17:00</td>
<td>Yes, because of other potential benefits: C. Patrono, Italy</td>
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**16:50-17:10 State of Art:** The role of recombinant factor Vlla versus FEIBA in hemophilia with inhibitors

- G. Kenet, Israel

**17:10-17:30 State of Art:** Can global assays be used to predict response to hemostatic agents?

- Y. Dargaud, France

**17:30-17:45 3-year results from SPINART: Prolonged reduction of bleeding with prophylaxis using Bayer’s sucrose-formulated recombinant factor VIII**

- W. Hong, USA

**17:45-18:00 Efficacy of prophylaxis using a phenotype-guided dosing strategy with BAY 94-9027: Results of a phase 2/3 multicenter, partially randomized, open-label trial (protect VIII)**

- L. Michaels, USA
Congress on Controversies in Thrombosis & Hemostasis

Posters
P01  INTERMITTENT PNEUMATIC COMPRESSION DEVICE FOR THE PREVENTION OF DEEP VEIN THROMBOSIS
Khaled Asfar, Jordan

P02  THE ASSOCIATION BETWEEN VENOUS THROMBOEMBOLISM AND LIPID PROFILE
Assia Benbraiek, Tunisia

P03  THE EFFECTS OF THE DOACS DABIGATRAN, RIVAROXABAN AND APIXABAN ON PLATELET FUNCTION TESTS
Ingvild Birschmann, Germany

P04  FRACTAL DIMENSION (DF) CORRELATES WITH INTERNATIONAL SOCIETY OF THROMBOSIS AND HAEMOSTASIS DIC SCORE IN PATIENTS WITH SIRS AND SEPSIS
Gareth Davies, UK

P05  CAN A RELAPSING INHIBITOR BE PART OF AN OVERACTIVE IMMUNE RESPONSE?
Marina Economou, Greece

P06  INHIBITORS IN HEMOPHILIA: A SINGLE CENTER EXPERIENCE
Marina Economou, Greece

P07  TISSUE FACTOR GENE -603 A/G AND +5466A>G POLYMORPHISMS ARE NOT ASSOCIATED WITH VENOUS THROMBOEMBOLISM IN CANCER PATIENTS
Aydan Eroglu, Turkey

P08  DEEP VENOUS THROMBOSIS AND QUALITY OF LIFE DURING PREGNANCY
Pavlos Sarafis, Greece

P09  IN VITRO CHARACTERIZATION OF THE ANTITHROMBOTIC FINGERPRINT OF THE BRANDED AND COPIES OF THE LMWH ENOXAPARIN
Grigoris T. Gerotziafas, France

P10  POLYMORPHISMS RS1800790, RS6046 AND RS5985 AND THEIR ASSOCIATION WITH ISCHEMIC STROKE. A CASE-CONTROL STUDY IN VENEZUELA
Jessyca Alexandra Gonzalez, Venezuela

P11  THE EFFECT OF LOWER LIMB IMMOBILISATION ON CALF PUMP FUNCTION
Edward Holloway, UK

P12  LOW-DOSE RECOMBINANT ACTIVATED FVII IN THE MANAGEMENT OF INTRACTABLE BLEEDING AFTER MAJOR SURGERY: A SINGLE CENTRE EXPERIENCE
Pavol Holly, Slovakia

P13  SPINART TRIAL 3-YEAR RESULTS WITH BAYER’S SUCROSE-FORMULATED RECOMBINANT FACTOR VIII: IMPROVED JOINT FUNCTION AND HEALTH-RELATED QUALITY OF LIFE IN ADULTS USING PROPHYLAXIS
Walter Hong, USA

P14  JOINT OUTCOMES BY MAGNETIC RESONANCE IMAGING AFTER TREATMENT WITH BAYER’S SUCROSE-FORMULATED RECOMBINANT FACTOR VIII IN THE SPINART STUDY: RESULTS AT THE 3-YEAR EVALUATION TIMEPOINT
Walter Hong, USA

P15  UPPER EXTREMITY DEEP VENOUS THROMBOSIS - PREVALENCE AND RISK FACTORS
Mihaela Hostiuc, Romania

P16  GENETIC RISK FACTORS ON ATHEROTHROMBOTIC DISEASE: COMPARISON BETWEEN TWO TERRITORIES
Irma Isordia-Salas, Mexico

P17  THE ANGIOTENSIN-CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM IS ASSOCIATED WITH INCREASED RISK FOR IDIOPATHIC ISCHEMIC STROKE BUT NOT FOR MYOCARDIAL INFARCTION IN YOUNG MEXICAN POPULATION
Irma Isordia-Salas, Mexico

P18  SUPERIORITY OF PROPHYLAXIS VERSUS ON-DEMAND THERAPY WITH PLASMA PROTEIN-FREE RECOMBINANT FACTOR VIII FORMULATED WITH SUCROSE (BAY 81-8973): LEOPOLD II STUDY RESULTS
Kaan Kavakli, Turkey

P19  SIMPLIFIED CRB-65 FOR RISK STRATIFICATION AND PREDICTING PROGNOSIS IN ACUTE PULMONARY EMBOLISM
Karsten Keller, Germany

P20  CARDIAC TROPNIN I FOR PREDICTING RIGHT VENTRICULAR DYSFUNCTION AND INTERMEDIATE RISK IN PATIENTS WITH NORMOTENSIVE PULMONARY EMBOLISM
Karsten Keller, Germany
P21 COMPARISON OF PHARMACODYNAMICS BETWEEN LOW DOSE TICAGRELOR AND CLOPIDOGREL AFTER LOADING AND MAINTENANCE DOSES IN HEALTHY KOREAN SUBJECTS
Moo Hyun Kim, Korea

P22 THE RELATION BETWEEN HIGHLY-SENSITIVE TROJON-I AND MEAN PLATELET VOLUME IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
Nermina Klapuh Bukvi, Bosnia and Herzegovina

P23 FREQUENCY AND NATURE OF NON-COMPLIANT SAMPLES FOR COAGULATION TESTING
Sandra Margetic, Croatia

P24 ANALYSIS OF FACTOR VIII ACTIVITY IN PATIENTS REFERRED FOR THROMBOPHILIA TESTING
Sandra Margetic, Croatia

P25 ANTIPLATELET DRUG RESISTANCE IN ASIAN POPULATION
Sadath Ambalath Pareed, India

P26 D-DIMER KINETICS, CHEMOTHERAPY AND THE RISK OF BLEEDING IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA
Namrata Peswani, USA

P27 VENOUS THROMBOEMBOLISM PROPHYLAXIS IN INTENSIVE CARE UNIT PATIENTS: FINDINGS OF THE BRAZILIAN REGISTRY
Ana Thereza Cavalcanti Rocha, Brazil

P28 COMPARISON OF VENOUS THROMBOEMBOLISM RISK-ASSESSMENT TOOLS FOR MEDICAL PATIENTS: PADUA SCORE VS. BRAZILIAN GUIDELINE ALGORITHM
Ana Thereza Cavalcanti Rocha, Brazil

P29 SUBSEQUENT CLOT PROPERTIES DEPEND ON THE STORAGE TIME OF PLATELET CONCENTRATES
Eugene Roitman, Russia

P30 A NOVEL USE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN THE MANAGEMENT OF PROSTHETIC VALVE THROMBOSIS DURING PREGNANCY
Katharina Schulte, Germany

P31 SAFETY AND EFFICACY OF BAY 81-8973 FOR PROPHYLAXIS AND TREATMENT OF BLEEDS IN PREVIOUSLY TREATED CHILDREN WITH SEVERE HEMOPHILIA A: RESULTS OF THE LEOPOLD KIDS STUDY, PART A
Anita Shah, USA

P32 PHARMACOKINETICS OF BAY 81-8973 DURING PROPHYLACTIC TREATMENT OF PATIENTS WITH SEVERE HEMOPHILIA A IN THE LEOPOLD TRIALS
Anita Shah, USA

P33 ANALYSIS OF CARDIOEMBOLIC STROKE SEVERITY AT ONSET AND PRIOR ANTITHROMBOTIC THERAPY
Andrian Sleptcov, Russia

P34 AIRWAY OBSTRUCTION BY BLOOD CLOT IN A CHILD: ROLE OF FLEXIBLE BRONCHOSCOPY
Francesca Savina, Italy

P35 ASSESSMENT OF IN VIVO ADMINISTERED RECOMBINANT ACTIVATED FACTOR VII BY THROMBIN GENERATION; EVALUATION OF THE MOST SUITABLE ASSAY METHOD
Camilla Stenmo, Denmark
INVITED LECTURES’ ABSTRACTS

S01
Friday, October 31, 09:20-09:40; Hall A
ROLE OF THROMBOPHILIA IN PREGNANCY COMPLICATIONS
Benjamin Brenner
Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus and Technion, Israel Institute of Technology, Haifa, Israel

Preeclampsia (PE), recurrent miscarriage, late pregnancy loss, fetal growth restriction, and placental abruption (PA) are commonly observed gestational complications, frequently sharing pathophysiological features. Jointly, these disorders present in 10–20% of pregnancies and may be associated with poor maternal and fetal outcome. Recurrent pregnancy loss (RPL) affects 1–5% of women at the reproductive age and has essential emotional, social, and economic impact. The hemostatic system plays a significant role in these pathologies. For example, coagulation activation occurs and fibrin deposition is revealed in small vessels in patients with PE and PA and in placentas of women with intrauterine fetal death.

Thrombophilic Risk Factors: Thrombophilic risk factors may be found in 15–25% of Caucasian populations. As pregnancy is an acquired hypercoagulable state, women harboring thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation. Several case-control and cohort studies have suggested an association between inherited thrombophilia and RPL (1-3). Some meta-analyses support an association between pregnancy loss and maternal factor V Leiden (FVL), and factor II G20210A genotypes (4-6). Multivariate analysis of findings obtained in the “NOHA first” study, including a cohort of almost 32,700 women, 18% of whom had pregnancy loss in first gestation, has revealed an association between unexplained first pregnancy loss after 10 weeks of gestation and the two thrombophilic risk factors (odds ratio, OR = 3.46 and OR = 2.60, respectively) (7). Similarly, PE was found to be associated with FVL or prothrombin mutation (PTM) and homozygous MTHFR C677T, with mean OR around 2. In a large Finish study of 100,000 consecutive pregnancies, the risk of late preterm birth was found to be 3 times higher in FVL carriers, but not in women with prothrombin polymorphism (8). The data of the Danish nested case-cohort study also showed that FVL increased the risk of late pregnancy complications (9). A recent meta-analysis of prospective cohort studies demonstrated that the likelihood of pregnancy loss was about 50% higher in FVL women (10); however, even this meta-analysis lacked power to detect increased risks in women with prothrombin mutation (PTM). Thus, the current notion is that, while thrombophilias are not the major cause of pregnancy complications, they may have a role in the miscarriage potential. The TREATS study found the risk of PE to be associated with F5 G1691A or F2 G20210A and homozygous MTHFR C677T, with mean odds ratios (OR) around 2(11). The paucity of information regarding antithrombin, protein C or protein S deficiencies limited statistical evaluation of association (11). A more recent systematic review, focusing on prospective cohort studies, revealed no significant association of PE with F5 G1691A and F2 G20210A (10).

Antiphospholipid syndrome: Fetal loss after week 10 and recurrent consecutive embryonic losses before week 10 are characteristic features of antiphospholipid syndrome (APS). Retrospective analyses revealed a stronger association with recurrent fetal loss >10 weeks in women positive for all the three tests (12). Women with APS often present with RPL and/or late pregnancy complications. An association has been reported between thrombophilic risk factors and pregnancy complications. A beneficial role of antithrombotic agents in preventing late pregnancy loss in this clinical setting has been suggested. A recent meta-analysis of the association between various antiphospholipid antibodies and placenta-mediated complications found the specific published reports to be frequently underpowered (13). These data provide biologic plausibility for a potential role of the hemostatic system in poor pregnancy outcomes. Thrombophilia may have an impact in cases where the pregnancy outcome is a consequence of impaired hemostasis, but screening for specific thrombophilias in the absence of information regarding the true disease process cannot be accurate (11). Hence, it is vital to explore these relationships in the context of the underlying disease process to improve the diagnosis and management of women with gestational vascular complications (14).

References:
The role of thrombophilia in pregnancy complications is a controversy in thrombosis and hemostasis. I will debate that the conclusion of efficacy of an intervention on. Second, beneficial effects of antithrombotic agents have been suggested by results from observational studies that have intrinsic methodological issues undermining their validity to assess efficacy of an intervention. Third, although some clinical trials have been performed in recent years, these are limited by strikingly small sample sizes and often lack a control arm without active intervention. Furthermore, study populations vary widely, with some trials using stringent inclusion criteria limiting the generalizability of the findings to women with other or coexisting complications; other trials using very broad inclusion criteria, making it difficult to draw conclusions for women with thrombophilia.

**Summary of randomized controlled trials and meta-analyses:** Aspirin to prevent pregnancy loss in APS - In women with APS, the pooled results of three very small trials showed no effect of aspirin only as compared to no treatment (RR of pregnancy loss of 1.05, 95% CI 0.66 – 1.68), but from the 95% CI it can be concluded that neither benefit nor harm can be ruled out.12 No randomized controlled trials evaluating the efficacy of aspirin in women with inherited thrombophilia and recurrent pregnancy loss have been performed. Aspirin to prevent preeclampsia - Although meta-analyses showed that aspirin was associated with a 10% relative risk reduction in preeclampsia, premature birth (less than 34 weeks gestation), and a pregnancy with a serious adverse outcome,13,14, no particular subgroup of women who were more or less likely to benefit from antplatelet agents could be identified. Heparin, with or without aspirin, to prevent pregnancy loss. A meta-analysis summarized the data of two studies in women with APS and two or more pregnancy losses;15 treatment with unfractionated heparin combined with aspirin reduced the chance of first trimester miscarriage when compared to aspirin only (RR 0.26, 95% CI 0.14 – 0.48); treatment with LMWH combined with aspirin compared to aspirin only showed a pooled non-significant risk reduction for pregnancy loss (RR 0.70; 95% CI 0.34 to 1.45). For women with recurrent miscarriage and inherited thrombophilia, no sufficiently sized trials have been performed that show an effect of heparin on the prognosis of a subsequent pregnancy. The Habenox trial, that did not include a no intervention arm, randomized women with at least three consecutive first trimester miscarriages to enoxaparin and placebo, enoxaparin and aspirin, or aspirin.16 There were no statistically different effects between the treatment groups. Another clinical trial allocated women with a single previous pregnancy loss after 10 weeks gestation who had heterozygous factor V Leiden mutation, prothrombin G20210A mutation, or protein S deficiency, to enoxaparin 40 mg or to aspirin.17 There was a large effect of enoxaparin compared to aspirin on live birth (86% and 29% respectively, odds ratio 15.5, 95%CI 7 to 34); however, several methodological issues were raised, and the results have not been confirmed by other trials.18,19 In the SPIN and ALIFE studies that investigated the effect of aspirin with or without LMWH in women with unexplained recurrent miscarriage, about 15% of women had inherited thrombophilia.20,21 In the ALIFE study, a modest non-significant increase in live birth was observed in the two active treatment arms for women with inherited thrombophilia (RR for live birth 1.22, 95% CI 0.69 to 2.16 for aspirin, and 1.31, 95% CI 0.74 to 2.33 for aspirin combined with nadropran, as compared to placebo), highlighting the urgent need for new randomized controlled trials. We are currently performing the ALIFE2 study (www.trialregister.nl, NTR 3361) that started recruiting in 2013; in this trial, women with inherited thrombophilia and recurrent pregnancy loss are being randomized to either treatment with LMWH plus standard pregnancy surveillance or standard pregnancy surveillance only.

**Heparin to prevent preeclampsia:** A few trials have investigated the use of LMWH with or without aspirin compared to no treatment in women with a history of various pregnancy complications. These six studies were recently summarized in a meta-analysis.11 The primary outcome was a composite of preeclampsia, birth of a small for gestational age newborn (<10th percentile), placental abruption, or pregnancy loss later than 20 weeks. The pooled risk reduction was statistically significant (RR 0.52, 95% CI 0.32-0.86), but clearly showed statistical heterogeneity (I2 69%). The included studies were relatively small, heterogeneous with regard to type of complications and the...
inclusion or exclusion of thrombophilia. The results were strikingly positive in some studies with relative risk reductions up to 85% 

22-24 whereas in the two most recently published studies in thrombophilic women, no effect on the risk of recurrence of severe pregnancy complications was observed.22,23 in all pooled studies combined, 25% of women had thrombophilia, and only the FRUIT study was dedicated to thrombophilic women only.25 In this trial, that randomized women with inherited thrombophilia and a history of preeclampsia or intra-uterine growth restriction, or weight <10th percentile requiring delivery before 34 weeks of gestation, between dalteparin with aspirin to aspirin alone. The primary outcomes were recurrence of a hypertensive disorder before 32 weeks gestation or recurrence at any gestational age. There was no difference between the 2 groups (risk difference 3.1%, 95% CI -10.5-16.7%). The recently finished TIPPS study that also included thrombophilic women only, either at high risk for pregnancy mediated complications or at high risk of pregnancy-related venous thromboembolism, randomized women between dalteparin and no dalteparin, and found no effect of the intervention.26

Conclusion: At present, the association between thrombophilia and pregnancy complications is modest at most, and intervention studies have not clearly and unequivocally shown the benefit of LMWH with or without the addition of aspirin. Hence, I regard the role of thrombophilia as minor, even though ongoing studies remain urgently needed and may prove otherwise if interventions show a differential effect of interventions in thrombophilic women.

References


monitoring of the anticoagulation effect, narrow therapeutic window, which is difficult to consistently maintain, and multiple interactions with other drugs as well as food substances. For these reasons novel oral anticoagulants (NOACS) have been developed and introduced into clinical practice in recent years. The 3 NOACS – dabigatran (thrombin inhibitor), rivaroxaban and apixaban (both factor Xa inhibitors) have all been tested in large phase 3 studies (vs warfarin) and are all approved by the FDA for the treatment of patients with non-valvular atrial fibrillation. All 3 NOACS have clear advantages over VKA – they do not require monitoring of the anti-coagulant effect and they have much fewer drug-drug interactions than VKAs. Most importantly, based on the large phase 3 studies, all 3 drugs have been shown to be at least as effective as warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation, and at least safe as warfarin in terms of the risk for major bleeding during treatment. Furthermore, treatment with all 3 drugs has been shown to be associated with a reduced risk of intracranial hemorrhage compared to warfarin. Thus, the risk-benefit ratio of all 3 NOACS is superior to warfarin in patients with non-valvular fibrillation. The advantages of NOACS for treatment of patients with atrial fibrillation, as well as specific properties of the 3 drugs will be discussed in the lecture.

S04
Friday, October 31, 12:20-12:40; Hall A
LABORATORY EVALUATION OF DOAC: DO’S AND DON’T’S
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For more than half a century, phenprocoumon and warfarin have been the drugs of choice for long-term anticoagulation, although their use is associated with several problems. This is why selectively acting anticoagulants, including a direct thrombin inhibitor (dabigatran) and two factor Xa inhibitors (rivaroxaban, apixaban) have been developed. These direct oral anticoagulants (DOACs: apixaban, dabigatran, rivaroxaban) permit the use of fixed dosing schemes. Due to the reliable pharmacokinetics and pharmacodynamics, no routine laboratory monitoring is necessary, although dedicated laboratory assays are available in situations such as thrombotic events or bleeding complications, the need for urgent surgery or suspected overdose.

The influences of DOACs on routine coagulation assays have been described in several publications. For example, the effect on prothrombin time (PT) and activated partial thromboplastin time (aPTT) has been evaluated using various reagents, various applications and a wide range of laboratory instruments. Both PT and aPTT show a positive dose response to increased DOAC concentrations, but responsiveness varies based on the screening test and reagent. Monitoring of the drugs can be done via clotting assays (diluted thrombin time, ecarin clotting time), chromogenic assays or liquid chromatography-mass spectrometry. This talk will discuss data concerning the influences of DOACs on the point-of-care testing (POCT) parameters routinely used for hemostatic analysis: activated clotting time (ACT) and thromboelastometry (ROTEM®). As POCT based on these two techniques is used regularly for evaluating global hemostasis during the perioperative phase, it is relevant to know the effects of anticoagulants. No dose-dependent changes in ROTEM® parameters or ACT could be tested. In principle, normal values of ACT and ROTEM® do not rule out the presence of these drugs. Furthermore, the effects of therapeutic concentrations of the drugs on light transmission aggeregometry, Multiplate® and PFA® are shown. As no effects may be observed, the platelet function tests can be performed independently from the through levels and the time of intake of the drug. Finally, the session will depict typical pitfalls in determination of the drugs and their interference with laboratory tests.

S05
Friday, October 31, 11:00-11:20; Hall B
EPIDEMIOLOGY AND RISK FACTORS OF VENOUS THROMBOSIS IN CHILDREN
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Introduction: Venous thromboembolic disease is an uncommon disease in childhood. Whereas the incidence in adults is about 10 per 10 000 persons per year, pediatric registries estimated the annual incidence in children to be 0.07 to 0.14 per 10 000 children. (1, 2) However, the incidence of pediatric thrombosis is increasing, which is caused by an increase in the survival of children with previously incurable diseases due to medical improvements in surgical interventions, treatment and supportive care. In childhood there are two age-related frequency peaks: the first peak is during the neonatal period, followed by another peak in adolescence, with a higher frequency in females, probably as result of the use of oral contraceptives. (3) The relatively high incidence of thrombosis in neonates compared to older children may be the result of small vessel size as most neonatal thrombi are catheter-related. In adolescents, the incidence is the same as that in young adults.

Neonatal thrombosis: In neonates, thrombosis is predominantly caused by the insertion of central venous catheters. In the Canadian and Dutch registry studies, 89% and 94% of neonatal thrombi were related to the use of a catheter, respectively. (1, 2) The thrombi are mostly located in the hepatic system, right atrium and superior/inferior vena cava. (4) Symptoms of neonatal catheter-related thrombosis include distal anwelling, sequential persistent thrombocytopenia. Diagnosis is usually made by color Doppler ultrasonography or echocardiography. Renal vein thrombosis is the most frequent non-catheter-related thromboembolism in the neonatal period. In the nineties, the incidence of symptomatic neonatal renal vein thrombosis was reported to be 2.2 per 100.000 live births in Germany. (5) About 7% of the neonates presented in utero, explaining the manifestation of inferior vena cava or renal vein calcification. (6) The precise pathophysiology is still unclear. Risk factors include prematurity, perinatal asphyxia, maternal diabetes mellitus, dehydration and infection. Probably, these risk factors cause a reduction in perfusion of the kidney, leading to vasoconstriction and drop in venous blood flow, thus increasing the risk of thrombosis. Most of the neonatal renal vein thrombi are unilateral, with a left-sided predominance. In about 40% of the patients, thrombi extended into the inferior vena cava. Symptoms included haematuria, palpable flank mass and thrombocytopenia. Long-term consequences such as hypertension, renal atrophy and chronic renal insufficiency may occur frequently. There is no clear consensus for the management of both catheter-related thrombosis and renal vein thrombosis in neonates.
**Thrombosis in older children:** In contrast to adults, idiopathic thrombotic events in children are rare. In three pediatric registries, only 2 to 8.5% of the children developed idiopathic thrombi. (3) Most of these idiopathic thrombi were observed in adolescents. The majority of thrombosis in children are related to central venous catheters: 33 to 48% of the children with thrombosis in the registries. As a consequence, there is a high incidence of upper extremity thrombosis in children. Other risk factors include sepsis, malignancy and surgery. More than 20% of the children have more than one clinical risk factor. The role of inherited thrombophilia in the development of pediatric thrombosis is not completely elucidated. A meta-analysis showed that inherited thrombophilia contribute to the development of pediatric thrombosis, in general. (7) However, routine testing in children with only one episode of thrombosis, especially those associated with a clear etiological factor, remains controversial. Especially, as results do not commonly change the management of the patient. Treatment of thrombosis consists of 3 to 6 months of anticoagulant therapy. (8) Anticoagulation, including low-molecular-weight heparin subcutaneously or unfractionated heparin intravenously, is the main initial therapy. The aims of initial anticoagulant therapy are to prevent thrombus extension and subsequent (pulmonary) embolization. In selected patients, usually children with extensive thrombosis, thrombolytic therapy might be an option, but there is a high risk of bleeding. Retrospective case series revealed bleeding complications to occur in up to 40% of the children treated with alteplase. (9) After initial anticoagulant therapy, both vitamin K antagonists and LMWH can be used for long-term anticoagulation in patients with thrombosis to prevent recurrent venous thrombosis, thereby reducing the risk of post thrombotic syndrome.

**Prophylaxis:** Despite the increasing incidence of thrombosis, thromboprophylaxis is not common practice in children. As most thrombi in neonates and children are associated with clinical risk factors, thromboprophylaxis strategies should be focused on these patient groups. Therefore, the first step towards thromboprophylaxis is to identify pediatric patients at high risk for thrombosis. Subsequently, trials are needed to investigate the efficacy and safety of thromboprophylaxis in these patients at risk. At this time, there is very limited data on the use of thromboprophylaxis in children and therefore, the risk/benefit ratio for thromboprophylaxis needs consideration on an individual patient basis.

**Conclusion:** Pediatric VTE is an uncommon disease but incidence is increasing. It usually occurs as a secondary complication in children with chronic diseases. To decrease the incidence of this complication preventive strategies in children at risk for thrombosis are urgently needed.

Reference List:

**SO6**
Friday, October 31, 11:40-12:00; Hall B
**SHOULD INFANTS WITH PERINATAL THROMBOSIS BE SCREENED FOR THROMBOPHILIA AND TREATED BY ANTICOAGULANTS?—NO**
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Perinatal stroke, defined as an insult occurring from 20 weeks gestational age, including in utero, to 28 days post nataly, is reported to occur in one in 2,300 to one in 5,000 live infant births. Subcategories within perinatal stroke include neonatal arterial ischemic stroke, neonatal cerebral sinus venous ischemic stroke, and presumed perinatal stroke. Perinatal arterial ischemic stroke (PAIS) has been defined more specifically by the National Institute of Health (NIH) Workshop on Perinatal Stroke as a condition with acute encephalopathy, seizures, or neurologic deficit presenting in a term or preterm infant before the 29th postnatal day, with brain imaging confirming a parenchymal infarct in the appropriate arterial territory (1, 2). The estimated mortality of neonatal stroke is 3.49/100,000 annually. Long-term outcome studies suggest that 60–80% of all infants develop some kind of deficit including motor impairments, abnormal cognitive outcome and post-neonatal epilepsy (3). The topic of this discussion is whether testing for thrombophilia and/or treating with anticoagulant has a beneficial effect on the outcome of children with PAIS. Perinatal arterial stroke is the result of a synergism of fetal and maternal factors. It is generally thought that the patent foramen ovale (PFO) allows passage of thrombi derived from the placenta or venous circulation, resulting in occlusion of an artery (2). Studies of children with a history of PAIS have reported prothrombotic factors in more than half of the population studied. In 91 consecutively recruited children with PAIS, prothrombotic factors were found in 68% of cases compared to 24% in age and sex-matched controls (4). In 60 mother-child pairs of infants with PAIS, prothrombotic risk factors were found in 55/81 mothers (55%) and 30/60 children (50%) (5). In another study of 23 mother and child pairs, at least one thrombophilic risk factor was found in 18 (78%) pairs (6). In a study of 24 infants with PAIS, 10 (42%) had at least one prothrombotic risk factor. In this study it was suggested that presence of the factor V Leiden mutation is associated with poor outcomes (7). Presence of antiphospholipid antibodies in the mother and/or infant was also associated to PAIS (6, 8-10). However, the development of PAIS seems not to be associated exclusively with inherited and acquired thrombophilia. Its etiology may be linked to perinatal events. Pregnancy is considered to be a natural prothrombotic state associated with changes in hemostasis due to evolutionary changes which protect the pregnant mother from fatal hemorrhage at delivery. These changes predispose the mother to...
thromboembolism and place the fetus and the placenta at risk for thromboembolic events. Maternal risk factors for PAIS include infertility, primiparity, maternal fever, meconium-stained amniotic fluid, chorioamnionitis, pre-eclampsia and intrauterine growth retardation (11, 12). Complicated deliveries, both instrumental and emergency caesarean section, low Apgar scores and hypoglycaemia are more frequently observed in infants with PAIS (11-13). Other triggering factors such as neonatal sepsis, perinatal asphyxia, or PFO may also potentiate the risk of PAIS (3). Infants with congenital heart disease are at a higher risk for PAIS, although the incidence is not clearly known. Additionally, there is an increased incidence of PAIS in the setting of cardiac surgery. Symptomatic recurrent thromboembolism is not common in children with PAIS (~3%) (14). Additionally, in infants with PAIS and positive antiphospholipid antibodies no recurrent thrombosis was recorded despite lack of prolonged anticoagulation (9). Recurrence rates may be higher in neonates with congenital heart disease, presumably due to a combination of factors including the type of congenital heart disease, the peri-operative cardiovascular status of the neonate, and the potential risk of complication from the needed surgical interventions such as cardiac reconstruction or cardiac bypass (3). A meta-analysis summarizing case control and cohort studies of PAIS revealed that positive thrombophilia screening was not associated with long term outcome and recurrence risk (15). During the acute phase, therapeutic options are limited and mainly involve supportive measures, such as maintenance of normal temperature, normal hydration, electrolytes, and glucose, hemoglobin, oxygen and pH levels (16). Treatment of clinical or subclinical seizures is recommended. Development of early intervention approaches for infants with unilateral PAIS are needed to improve outcome (17). As no benefit was shown for anticoagulation in the setting of acute PAIS, the role of anticoagulation is limited for neonates with first PAIS in the presence of an ongoing cardio-embolic source and for neonates with recurrent PAIS (18). Prior to testing children for inherited thrombophilia, clinicians should consider whether testing can improve clinical outcomes (19). Ethical guidelines suggest that a medical benefit, related to therapy or prevention, should be the primary justification for genetic testing in children and adolescents (20). Thus, current available data does not support routine thrombophilia testing of infants with PAIS. Testing for thrombophilia should probably be reserved for those with significant multisystem thrombosis or for those with significant family history. In those rare cases, positive laboratory results consistent with thrombophilia may affect decisions regarding the need and/or duration of anticoagulation therapy. When counselling parents with regard to subsequent pregnancies, testing the mother for persistently elevated antiphospholipid antibodies may be considered (21).

References:
IS THERE A ROLE FOR PRIMARY ANTICOAGULANT PROPHYLAXIS IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKAEMIA? - NO

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Introduction: Symptomatic and asymptomatic venous thromboembolic events (VTE) are important complications in children with cancer, especially in children with acute lymphoblastic leukemia (ALL). The question is whether there is a role for primary thromboprophylaxis in these patients to minimize mortality and morbidity caused by VTE and further improve cancer survival rates.

Epidemiology and risk factors: In children with ALL the incidence of VTE varies between 1.2% and 36.7%. (1) This discrepancy is caused by variation in definition of VTE (symptomatic or asymptomatic), the study design (retrospective and prospective) and treatment protocols. For example, in the Netherlands the thrombotic risk appeared to be higher in children treated according to the Dutch Childhood Oncology Group (DCOG) ALL10 protocol including low doses of asparaginase and prednisone than children treated according to the DCGO ALL9 protocol including high doses of asparaginase over a shorter period and dexamethasone. (2) VTEs usually occur in the central nervous system and in the upper limbs, the latter due to association with central venous catheters. (3) Several factors contribute to the development of thrombosis in children with ALL, including the primary disease itself, treatment of the disease, complications of treatment, and host-associated factors. At diagnosis the thrombin generation is increased in children with ALL. Blood coagulation can be activated by the primary disease via procoagulant substances or by loss of thromboembolic proteins, especially antithrombin (AT) are reduced by decreased protein synthesis gives rise to the associated toxicities, as well. Both coagulation factors and anticoagulant proteins, especially antithrombin (AT) are reduced by asparaginase. Asparaginase is an important element of pediatric protocols to treat ALL. Asparaginase catalyzes the hydrolysis of asparagine to aspartic acid and ammonia and thus depletes the asparagine pool. Lack of asparagine reduces protein synthesis and cell proliferation, which results in cytotoxicity of the lymphoblasts. Decreased protein synthesis gives rise to the associated toxicities, as well. Both coagulation factors and anticoagulant proteins, especially antithrombin (AT) are reduced by asparaginase. Furthermore, asparaginase activates white cells and endothelium causing thrombin initiation and up regulation of tissue factor. Escherichia coli asparaginase is superior over Erwinia asparaginase as an antileukemic agent but at the cost of increased toxicity, including thrombotic events. (4) Steroids enhance the hypercoagulable state by elevation of Factor VIII/ von Willebrand factor complex and by causing a hypofibrinolytic state due to increase of plasminogen activator inhibitor 1. (5) Prednisone seems to have a higher thrombotic effect than dexamethasone. Higher dosages of steroids might increase the thrombotic risk, as well. (6) In addition to chemotherapy, therapy-associated factors, such as the insertion of catheters and infection may increase the thrombotic risk. The risk of catheter-related thrombosis is higher when the catheter is inserted on the left side of the body, in the subclavian vein and by percutaneous technique. (7) Finally, host-associated factors may influence the risk of thrombosis, such as inherited thrombophilia. The extent of this contribution, however, is unknown and prospective studies reported conflicting results. Until now, it is unclear whether identification of thrombophilia is necessary to guide prophylactic strategies.

Consequences of thrombosis: Morbidity and mortality of thrombotic events in children with ALL are not well studied. Reported mortality varied between 0 and 50% with an average of 15%. (1) Small studies reported residual neurological deficits in about 15 to 20% of the pediatric ALL patients with sinovenous thrombosis. (8, 9) Finally, thrombotic events may influence the outcome of cancer. The asparaginase-associated thrombi may cause delay or decrease of asparaginase therapy. Continuation of asparaginase therapy, however, is important in ALL patients for long term survival. (8, 10)

Prevention of thrombosis: Primary thromboprophylaxis includes replacement or anticoagulant therapy. As asparaginase causes acquired AT deficiency, fresh frozen plasma (FFP) or AT concentrates have been used to prevent thrombosis. However, AT levels did not rise and the number of thrombotic events did not decrease after supplementation of FFP in children with ALL during asparaginase treatment. (11) In addition, FFP may have significant disadvantages, such as allergic reactions, volume overload and the presence of asparagine. Small observational studies investigating AT replacement therapy in children with ALL were unsuccessful, as well. (12, 13) One prospective, randomized controlled trial (the PARKAA study) was performed studying the efficacy and safety of AT supplementation in children with ALL. (14) AT was administered once weekly for 4 weeks to increase AT plasma concentrations to about 30 IU/L during asparaginase treatment. VTE was present in 7 of the 25 patients (28%, 95%CI: 12.1%-49.4%) treated with AT concentrate versus 22 of 60 patients (36.7%, 95%CI: 24.4%-48.8%) without AT concentrate. The difference between the prevalence of VTE in both groups was not statistically different, but the study was only powered to detect a trend. A few studies have been performed studying prophylactic anticoagulation in pediatric cancer patients. A recent Cochrane review found no significant effects of systemic anticoagulant treatments compared with no intervention in preventing (a)symptomatic VTE in paediatric ALL patients with CVCs. (15) Mitchell et al. were the first to develop and validate a predictive model. (16) The potential risk factors for VTE in children with ALL used in this model were identified in the meta-analysis of Caruso et al. and included: (1) treatment with Escherichia coli asparaginase, (2) concomitant use of steroids, (3) presence of central venous catheter and (4) inherited prothrombotic disorders. In a pilot study, 8 of 19 consecutive children with ALL and high risk score received prophylactic LMWH, which started before catheter insertion and was administered until the end of induction therapy. The children with LMWH showed a significant better thrombosis free survival compared to the children without prophylactic LMWH. (p=0.023) No bleeding complications occurred. Al-Aridi et al., however, showed that the predictive model of Mitchell et al. might not be effective in all study populations and treatment protocols. (17)

Conclusion: The high VTE risk in combination with the significant burden of complications, seems to justify primary thromboprophylaxis in paediatric cancer patients. Nevertheless, there is not enough evidence to give prophylactic anticoagulation in all children with ALL. Large, multi-centre studies are necessary to investigate the efficacy and safety of prophylactic strategies, which should be tailored to treatment protocols and patient populations as result of variations in risk factors.
Reference List


Optimal prophylactic treatment should be started early (primary prophylaxis) but various opinions exist on when to start, the dose and dose interval, depending on the objective of treatment in the individual patient which in turn is usually dependent on the resources in the health care system. Ideally, prophylactic therapy of hemophilia should be offered to all boys with severe, and some with moderate, hemophilia and should be started around the age of one year before the onset of joint hemorrhage and, as soon as circumstances allow, be administered every second day in hemophilia A and every third day in hemophilia B. When to start? In my opinion it should be as early as possible which usually means around the age of one year. One argument against such a regimen is that approximately 10-15% of boys with severe hemophilia have a less severe phenotype with a low frequency of joint bleeds and one should wait to observe the bleeding frequency. However, waiting means that these boys still have the risk of traumatic hemorrhages and they have no protection against an intracranial hemorrhage (ICH). Several studies have shown that the risk of intracranial hemorrhage after the neonatal period is 20-50 times more frequent in a person with hemophilia without prophylactic treatment compared to a non-hemophilic. This is a fact that deserves more attention when discussing prophylactic treatment of hemophilia. Furthermore, it has been shown that once hemophilic arthropathy has started it may, at least in some susceptible individuals, progress despite adequate therapy. Another argument for an early start is that avoiding the “immunological danger signals from a concomitant bleed” may reduce the number of individuals developing antibodies. However, this could not be proved in a recent “proof of principle study” and the effect of age itself is itself and the dose of antibodies has been ruled out in other studies. A problem with an early start of regular prophylaxis is obviously venous access. In our own hands, about one third of the patients will need a central venous access device (CVAD) which will carry an approximately 25% risk of complications during its lifetime, most frequent are infections, catheter-associated thrombosis (usually subclinical) and technical problems. Introducing a CVAD is a risk that has to be balanced against the potential benefits in the individual patient. My advice is to start early treatment by use of a peripheral vein once per week and successively increase the frequency of infusions. If this approach does not work (which is usually obvious within a short time) and in particular if the child has frequent bleeds, it is usually easier for both the parents and the doctor to make a decision to implant a central venous catheter and to accept potential future complications of the device. Which dose and dose interval? If started at the age of one year, it is usually practical to start once/week and let the child, veins and parents get used to the new procedure. When circumstances allow, the goal is to administer every other day in hemophilia A and every third day in hemophilia B in all patients. A high frequency escalation regimen in which escalation is based on the bleeding frequency, and leaves a large proportion of

Friday, October 31, 14:20-14:40; Hall A

PROPHYLAXIS FOR CHILDREN WITH HEMOPHILIA SHOULD START EARLY OR AFTER JOINT BLEED? IS LOW DOSE REGIMEN PREFERABLE TO STANDARD DOSE?

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individuals on a once or twice/week prophylaxis, cannot be considered to be a “full prophylaxis” since the children will be unprotected several days of the week. Evaluation of such regimens has shown the development of target joints and significant joint changes on MR already in early childhood. The initial dose at the age of one should be 25 U/kg, i.e. a 250 U vial. There is no reason to administer 50 U/kg since it will only add a short period of time before the FVIIIC/XC is <1%. The argument against such a regimen, if venous access has been handled as suggested above, is primarily the cost. The cost accepted will depend on the objective of prophylactic therapy which can be mapped along a spectrum of treatment choices and, the healthcare resources in the specific country that can be allocated to hemophilia care. However, the economics of prophylaxis is mainly a political and not a medical question. At “the low end” of frequency and/or dose can even perform physical exercise on days when concentrate is administered. Another way to individualize treatment and optimize the savings of concentrate can be made by daily dosing which should be feasible in many patients after the early years with problematic venous access in childhood. In the near future we face a new situation when long acting FVIII/IX has reached the market. These concentrates will probably facilitate the start of prophylactic treatment but may not be the solution to all current obstacles. Today, the recommendation should be to start prophylaxis once a week around the age of one year but as soon as possible, even if a CVAD is needed, increase the frequency to every second/third day in, respectively, hemophilia A/B, the dose being dependent on the available resources in a spectrum from 10-25 U/kg/dose. 

Global tests of the haemostasis, such as aPTT and PT, are commonly used in the perioperative setting in the belief that these tests could identify patients with an increased bleeding risk. However, published evidence does not longer support this approach for both traditional screening tests and novel techniques of global assessment of haemostasis. Unselected laboratory screening yields many false positive results and detects irrelevant disorders such as FXII deficiency. It leads to postponement of surgery, anxiety in parents and patients, and is not cost effective. Even worse, it does not reliably detect relevant bleeding disorders such as the most common coagulopathy, von Willebrand disease. Rare, but sometimes relevant diseases such as thrombocytopenias are also missed, since adequate screening tests are not widely available outside of specialized centres. The bleeding history of patients and their relatives seems to be a more effective tool to detect patients at risk. According to international guidelines and a joint statement of different German medical societies, a standardized questionnaire should be mandatory in preoperative screening. A diagnostic pathway should be employed to identify patients in whom specific tests are helpful. To allow comparison of bleeding symptoms over time, scoring systems such as the ISTH-Bleeding Assessment Tool might be helpful. Because neither laboratory tests nor questionnaires can infallibly predict or exclude perioperative bleeding problems, guidelines for the management of these unexpected situations have to be established.

**S10**  
Friday, October 31, 15:30-15:50; Hall A  
**SHOULD WE SCREEN CHILDREN FOR COAGULOPATHIES PRIOR TO SURGERY?**  
Christopher Bidlingmaier  
Dr. v. Haunersches Kinderspital Klinikum der Universität München

Screening for coagulopathies prior to surgery in children may include some or all of the following: medical history, personal bleeding history, familial bleeding history, routine laboratory testing, i.e. complete blood count (CBC), activated partial thromboplastin time (aPTT) and prothrombin time (PT), specific blood coagulation testing and/or point of care (POC) testing. The topic of this discussion is whether the medical history, bleeding history and familial bleeding history are sufficient for predicting bleeding risk prior to surgery, or whether additional routine laboratory testing, specifically PT/aPTT, is necessary. Evidence for the utility of bleeding history alone for pre-surgical screening in children is inconclusive. In a study of 875 children prior to tonsillectomy, of 21 patients (2.5%) who had a personal or family history of abnormal bleeding, 5 (23.8%) were found to have a coagulopathy, but none bled following surgery (1). In the same study, postoperative bleeding occurred in 31 children (3.5%); in 22 (2.9%) of 748 children with normal PT/aPTT vs. 9 (7.1%) of the 127 with laboratory abnormality (p = 0.041). In another study of 792 children prior to tonsillectomy and adenoidectomy (T&A), a positive personal or family bleeding history was documented in 268 (34%) children. Only 17/32 (53%) children with potentially significant coagulation abnormalities, i.e. abnormal PT and/or aPTT, were found to have a positive bleeding history (2). The conclusion of this study was that bleeding history alone is insufficient and that routine preoperative coagulation testing may serve as a useful adjunct to clinical history. Similarly, a decision analysis model showed that no preoperative coagulation testing prior to T&A in children is the most cost effective, even when compared to selective testing of those with a pertinent history (3). Bleeding history in children may be misleading as challenges to the hemostatic system are often required to make a bleeding disorder clinically evident. Thus, a mild/moderate bleeding disorder may go undetected until events such as trauma, surgery, or menarche occur.

Use of a structured questionnaire to derive a bleeding score has been suggested to increase the predictive value of post-surgical bleeding (4). The utility of a preoperative bleeding questionnaire (POBQ) was studied in 7730 children prior to T&A. No difference in bleeding was seen between those with or without positive bleeding history (5). However, a difference was detected in bleeding rates among children with a positive coagulation screen as opposed to those with a negative coagulation screen (p = 0.005) (5). In contrast to the findings in children, in a study of 3041 tonsillectomies in adults, a positive history was significantly associated with a higher risk of postoperative bleeding (31%,
17/55, p < 0.002) compared to patients with a negative history (16 %, 387/2,497). A positive coagulopathy laboratory result was not significantly associated with an increased bleeding risk; (20 %, 19/94, p < 0.235) compared to patients with a negative laboratory result (16 %, 390/2,249) (6). Similarly in a large cohort of adult patients (>1800) undergoing neurosurgery, patient history was as predictive as laboratory testing for all outcomes, with higher sensitivity (7). Evidence for the utility of laboratory testing prior to surgery is likely related to the risk of bleeding and to the size of the study. Routine coagulation screening in 250 children undergoing gastrointestinal endoscopy did not predict those at risk of bleeding (8). In 355 children admitted to the neurosurgical department for elective procedures, routine coagulation screening increased the cost without any medical benefit (9). Similar results were shown in a study of 272 children undergoing T&A (10). The number of children (5 (1.8%)) having a major bleeding event was too small to show a difference between normal and abnormal coagulation studies. Preoperative coagulation screening tests provided low sensitivity and low bleeding predictive value in a study of 416 children undergoing T&A surgery with 66 children having a bleeding event (11) and in a study of 274 children with two children having a bleeding event (12). Larger studies or a meta-analysis of existing studies are needed to examine the prognostic value of preoperative coagulation testing in children. Post-surgical bleeding may be a devastating event for the child and the family and may be associated with significant morbidity, health care utilization, and expenditures. Post-surgical bleeding was the most common and most expensive complication after tonsillectomy in adults (13). On the other hand, children with coagulation disorders when evaluated and corrected preoperatively did not have an increased risk of post-tonsillectomy hemorrhage (14, 15). Unfortunately routine laboratory coagulation tests can miss underlying bleeding disorders. In a study of 1516 children who had T&A, 13 (0.8%) had immediate postoperative bleeding. Although all 13 bleeders had normal preoperative PT/aPTT, five of them were found to have mild von Willebrand disease (VWD) (16). Whether using the 1.17 upper limit of the aPTT will have a better sensitivity and a satisfactory specificity for identifying isolated von Willebrand factor deficiencies needs further confirmation (17). Screening with a platelet function analyzer (PFA) prior to surgery did not improve the diagnostic rate for VWD (18).

In summary, the utility of coagulation laboratory screening in children prior to surgery needs to be further studied, especially in procedures with a high risk of bleeding. Future studies should be prospective with large sample size, using a standardized pediatric bleeding questionnaire, laboratory coagulation screening and bleeding outcome assessment. Until those studies are available most physicians will elect to perform CBC and coagulation laboratory tests in children with high risk for bleeding and/or prior to surgical procedures involved with high risk of bleeding.

Reference:

511 Friday, October 31, 17:20-17:40; Hall A NEW ANTI-PLATELET AGENTS – ADVANTAGES Eli Lev Interventional Cardiology Unit, Hasharon Hospital, Rabin Medical Center, Petah-Tikva, Tel-Aviv University, Israel

Dual anti-platelet treatment with aspirin and an ADP P2Y12 receptor inhibitor is a central and crucial component of treatment of patients with acute coronary syndromes (ACS). For many years clopidogrel has been the ADP inhibitor of choice for treatment of patients with ACS, as well as patients undergoing percutaneous coronary intervention (PCI). However, treatment with clopidogrel is hampered by wide variability in response to the drug (with patients who show low response – high on treatment platelet reactivity – being at high risk for thrombotic adverse events), as well as by a slow onset of action. For these reasons new platelet ADP inhibitors have been developed – prasugrel and ticagrelor. Prasugrel is a 3rd generation thienopyridine, and ticagrelor is a direct acting reversible P2Y12 inhibitor. Both drugs have superior
pharmacodynamics properties to clopidogrel – a more rapid onset of action (effective platelet inhibition within about an hour compared to about 4 hours with clopidogrel), more potent platelet inhibition during the lading and maintenance phases, and most important, more consistent effect with very rare occurrence of high on treatment platelet reactivity (HTPR). These superior pharmacodynamic properties have been translated to clinical benefits. Both drugs have been compared to clopidogrel in large phase 3 studies in patients with high-risk ACS (mainly patients with ST- and non-ST segment myocardial infarction) – the TRITON study for prasugrel and PLATO study for ticagrelor. Both drugs have been found to be superior to clopidogrel in the prevention of the composite endpoint of cardiovascular mortality, myocardial infarction or stroke. Furthermore, both drugs reduced the risk of stent thrombosis in patients who underwent PCI with stenting. However, as expected from more potent antiplatelet drugs, the reduction in the risk of ischemic adverse events, came at the expense of an increased risk of bleeding. The specific pharmacodynamics and clinical advantages of both new drugs as well as population subsets who derive the most benefit or risk will be discussed in the lecture.

S12
Friday, October 31, 17:40-18:00; Hall A
NEW ANTIPLATELET AGENTS: LIMITATIONS
Alan D. Michelson
Harvard Medical School/Boston Children’s Hospital, Harvard Medical School/Brigham and Women’s Hospital

New, clinically-approved P2Y12 antagonists (prasugrel and ticagrelor) have pharmacodynamic and clinical advantages over previously available P2Y12 antagonists (clopidogrel) – but also some limitations.

Limitations of Prasugrel:

- In the definitive TRITON-TIMI 38 trial which led to the FDA approval of prasugrel, prasugrel's clinical benefit came with a higher incidence of hemorrhagic side effects, including life-threatening bleeding, than clopidogrel.
- Patients greater than 75 years of age and less than 65 kg received no benefit from prasugrel compared to clopidogrel, while patients with prior stroke or transient ischemic attack (TIA) experienced harm. Prasugrel is therefore contraindicated in patients with prior history of stroke or TIA, and is not recommended in patients greater than 75 years old or less than 65 kg.
- Cost.

Limitations of Ticagrelor:

- In the definitive PLATO trial which led to the FDA approval of ticagrelor, ticagrelor’s increased clinical benefit came with a higher incidence of hemorrhagic side effects than clopidogrel in non-CABG patients.
- The benefit of ticagrelor in PLATO was not observed in North American subjects, in whom the results favored clopidogrel.
- Ticagrelor must be administered twice daily, whereas aspirin, clopidogrel and prasugrel are all administered once daily.
- While the irreversible effects on platelets of aspirin, clopidogrel, and prasugrel make their effects difficult to turn off, this can be of potential benefit in the chronic outpatient setting by providing at least a partial buffer for occasional missed doses – which is not the case with ticagrelor, because of its reversible effect on platelets and its twice-daily administration.
- Ticagrelor results in a higher incidence than clopidogrel of dyspnea and ventricular pauses, but these symptoms are usually clinically insignificant. In the PLATO trial, dyspnea led to discontinuation of the study drug in 0.9% of ticagrelor-treated patients and in 0.1% of clopidogrel-treated patients. The excess of ventricular pauses was sinoatrial in origin and more frequently nocturnal.
- Cost.

S13
Friday, October 31, 16:30-16:50; Hall B
PATIENTS WITH FACTOR VII OR FACTOR XI DEFICIENCY; DO THEY NEED TREATMENT PRIOR TO SURGERY? YES
Paula HB Bolton-Maggs
Serious Hazards of Transfusion Office, Manchester Blood Centre, Manchester, UK

Where the relationship between a measured coagulation factor level and bleeding tendency is clear, for example hemophilia A or B, it has been straightforward to generate guidelines for the management of injury or for surgery. Haemophiliacs are conventionally classified by bleeding tendency and level as mild, moderate and severe. This classification does not work well for the rarer coagulation deficiencies, particularly for factors V, VII and XI. Although there is a tendency for patients with very low FXI levels to bleed after surgery, particularly in areas of fibrinolysis, this is not absolute, nor is it predictable from the family history or particular gene mutation, and there is no relationship between the FXI level and bleeding tendency in partial FXI deficiency 2, 3. Some guidance can be given 2,4, but better methods for predicting bleeding are required, and thrombin generation tests in platelet rich plasma with a low tissue factor level have a better correlation with bleeding history than the coagulation factor level and may provide a better assessment of whether FXI replacement is indicated 5. Fresh frozen plasma (FFP) can be used but carries the risk of volume overload. Two FXI concentrates are available but both have been associated with thrombotic events and should therefore be used cautiously, particularly in those at increased risk of thrombosis (elderly, vascular disease) 6, 7. Low dose FXI concentrate can be used for tonsillectomy in a young patient with very low level FXI, and the use of such replacement therapy should generally be accompanied by thromboprophylaxis. Some types of surgery, even in those with absent FXI, may proceed without FXI replacement using antifibrinolytic agents (e.g. dental extractions, hernia repair or other surgery with no raw bleeding areas left post-operatively 4). FFP and FXI concentrates are best avoided in patients with null mutations who are at increased risk of developing inhibitors: recombinant activated factor VII (rVIIa) has been used successfully in these patients 8. The situation with FVII deficiency is similar in that the relationship between the measured level and bleeding is poor. Factor VII deficiency is the most common of the rare coagulation disorders. The level required for haemostasis is generally much lower than in hemophilia and probably about 10 iu/dL so it is important not to over treat by using an inappropriate cut-off. The diagnosis should be made cautiously noting that different thromboplastins may give very different FVII levels (associated
with particular mutations). Human recombinant thromboplatin the is preferred reagent 9, 10. The clinical picture is very variable but registry analyses have been informative 11, 12. Completely absent FVII is associated with a definite bleeding risk including intracranial hemorrhage. Women with severe deficiency are likely to suffer menorrhagia which requires appropriate management with antifibrinolytics and hormone therapy. Surgery can be managed optimally with low dose rFVIIa at 15-30microg/kg as boluses or by continuous infusion (although not licensed by this route).

**Conclusion:** Patients with either FXI or FVII deficiency all require careful assessment prior to surgery to define the previous bleeding history (predictive in FVII deficiency), the nature of the surgery (e.g. tonsillectomy in FXI deficiency will require replacement therapy but appendectomy may not, regardless of the plasma FXI level) and the presence of additional risk factors for thrombosis particularly in FXI deficiency. Standard formulae cannot be applied. Other treatment may also be appropriate such as antifibrinolytic therapy alone (for dental extractions in FXI deficiency). In this sense, all patients with either FXI or FVII deficiency need “treatment” prior to surgery including discussion and counselling about the management, what to watch for afterwards and follow up.

**References:**


limit blood loss during liver transplant surgery, and its prophylactic use is common in some liver transplant centers. Treatment of active bleeding requires hemostatic treatment, except in cases in which the bleeding clearly has non-hemostatic causes (notably surgical bleeding and variceal bleeds). When hemostatic failure is the cause of active bleeding, supplementation of missing factors may be guided by standard laboratory tests or thromboelastography, although current approaches lack solid scientific evidence. Failure of primary hemostasis in a bleeding patient requires transfusion of platelet concentrates. Management of failing secondary hemostasis is unclear but may consist of factor concentrates (PCCs, fibrinogen) and/or plasma. Recombinant factor VIIa is not indicated, except as a ‘rescue’ agent. Antifibrinolytic agents are helpful in management of fibrinolytic bleeding.

Chronic liver disease, particularly in the end stage, is characterized by bleeding accompanied by decreased plasma levels of pro-coagulant factors, with the notable exception of factor VIII and von Willebrand factor which are high. Decreased levels of these pro-coagulants are, however, paralleled by the concomitant decrease of naturally occurring anti-coagulants (antithrombin, protein C, protein S and tissue factor pathway inhibitor). In physiological conditions, the coagulation system is balanced by these two opposing drivers, but the mechanistic significance of the parallel decrease of both pro- and anti-coagulants in chronic liver disease escaped attention for many years. As a consequence, this condition was considered the epitome of acquired bleeding disorders, and the basic laboratory tests that explore blood coagulation, i.e., the prothrombin and activated partial thromboplastin time, have been widely used to assess the risk of bleeding in liver disease according to the degree of their prolongation. However, their abnormal results are only poorly correlated with the onset and duration of bleeding following biopsy or other potentially hemorrhagic procedures. The prolongations of these tests were also poorly correlated with the occurrence of gastrointestinal bleeding, the prototype of hemorrhagic events in end-stage liver disease. Additional evidence that argues against the clinical relevance of conventional laboratory tests in determining the bleeding tendency of these patients can be drawn from the natural history of liver transplantation. In the past, this major surgical procedure carried out in patients with end-stage liver disease required massive transfusions of plasma and other blood products, that were prescribed to correct the multiple abnormalities of hemostasis tests observed both pre- and peri-operatively. The need for transfusion, however, declined considerably over time, and this was not due to any significant change in medication but rather to improved surgical procedures. Furthermore, randomized clinical trials have shown that a powerful hemostatic agent such as recombinant activated factor VII fails to reduce blood losses during liver transplantation, in spite of the fact that the post-infusion prothrombin time is considerably shortened. All this notwithstanding, it is a fact and deed that patients with end-stage liver disease do develop prominent and life-threatening bleeding symptoms, particularly in the gastrointestinal tract. Yet, the concept of considering this bleeding tendency solely on the basis of the abnormalities of conventional coagulation biomarkers does not hold true and should be reconsidered. When patients are investigated by means of global tests such as the thrombin generation test and thromboelastography hemostasis is rebalanced towards normal values even towards or hypercoagulability. Thus, the main culprits for the bleeding tendency observed in end-stage liver disease should be searched for among such underlying conditions that favor bleeding as portal hypertension, endothelial dysfunction, bacterial infections and renal failure. In conclusion, evidence of a rebalanced hemostasis challenges the dogma that coagulopathy in patients with chronic liver disease causes their bleeding symptoms, because in them the balance of anticoagulant and procoagulant factors is restored. Possible clinical implications of this hemostatic rebalance imply a caveat toward the unrestricted use of plasma infusion to correct the abnormalities of conventional coagulation tests in patients who are bleeding or must undergo invasive procedures. This is still a common practice, despite lack of evidence from controlled randomized trials and recent guidelines of the American Association for the Study of Liver Disease, which warn against the indiscriminate use of plasma therapy before liver biopsy. Recombinant activated factor VII, was shown to be of little or no clinical benefit in the control of esophageal bleeding, should not be used. Nor there is evidence that fibrinogen concentrates are of any usefulness, even in patients with low plasma levels of this procoagulant. Pertaining to fibrinolysis, the balance of this anti-hemostatic system is likely to be restored in chronic liver disease by concomitant changes in pro- and antifibrinolytic drivers. This is consistent with the conclusion of a Cochrane meta-analysis against the use of antifibrinolytic amino acids for upper gastrointestinal bleeding in acute and chronic liver disease. Pertaining to platelet transfusions, there is no evidence that they help to increase significantly the degree of thrombocytopenia in patients with liver cirrhosis.

While the incidence of thrombosis in children is increasing due to advances in both medical treatment and imaging technologies, the knowledge on treatment is still sparse. However, guidelines for the use of heparins and warfarin in children are available, although often adapted from adults and extrapolated from smaller studies, case series and the few randomized trials. Both treatment regimens and necessary monitoring of these “old” substances are still in the focus of an ongoing debate. The presented review will include remarks on the use of both heparins and warfarin in special clinical situations, such as prevention of CVL related thrombosis, prevention of posttraumatic and perioperative thrombosis or the use of the substances in special patient populations. Although desirable, properly powered and well-designed studies especially regarding the use of LMWH become less likely in the advent of the new anticoagulants and the ongoing clinical studies regarding these new substances. Despite this lack of evidence based data, LMWH can be judged safe and...
effective in most situations and will remain standard of care until robust data on new anticoagulants are available. This is also true for warfarin’s, which will accompany us for a long time, given the price differences between tis old and well characterized drug in comparison to both LMWH and newer substances.

| S17 | Saturday, November 1, 11:10-11:30; Hall B | NEW ORAL ANTICOAGULANTS IN CHILDREN: SHOULD THEY BE PRESCRIBED FOR SPECIAL (OFF LABEL) SITUATIONS? - NO | Alan D. Michelson | Harvard Medical School/Boston Children’s Hospital
Harvard Medical School/Brigham and Women’s Hospital

Heparin and warfarin are the traditional anticoagulants used to prevent thrombosis, but both agents are difficult to use effectively in the pediatric population.1 Recently, new oral anticoagulants (NOAC), both direct thrombin inhibitors and direct factor Xa inhibitors, have been developed and approved for an increasing number of adult patients (Table). The advantages of NOAC include their oral route of administration, rapid onset of action and few clinically important interactions with food or other medications. NOAC also have standardized dosing with no need for monitoring, although this has yet to be confirmed for pediatric populations.2 Furthermore, liquid formulations and their absorption leading to predictable drug levels need to be carefully studied in children. The clinical scenario for anticoagulation in children often differs from adults, and frequently includes indwelling catheters or mechanical valves— and none of the NOAC have been shown to effectively prevent thrombosis on these artificial surfaces.2 Although the use of NOAC is supported by evidence in adult patients, data are needed in children, beginning with appropriate pharmacologic and pharmacodynamic studies in neonates and children, and in pediatric clinical scenarios (Table).2 Extrapolations regarding efficacy and safety from adult studies are not appropriate in most relevant pediatric clinical situations, because of differing developmental aspects of hemostasis and because of the often differing clinical indications in children — although there are considerable challenges to performing pediatric-specific clinical trials. Specific study of the mechanisms of action of NOAC, and their impact on coagulation monitoring assays, are feasible in children and should be performed given the known and suspected developmental differences in the coagulation pathways between children and adults.2 The issues of bleeding and reversibility associated with NOAC will need to be evaluated less efficiently in pediatric clinical scenarios. Before NOAC are approved for pediatric use, European and North American regulatory agencies require pediatric investigational programs.2 Although there are multiple pediatric phase 1 studies in progress, recruitment has been very challenging because potential study subjects should be at risk for developing a thrombotic complication and may not directly benefit from intervention, despite the advantages of improved convenience and acceptability. The potential lack of benefit in the face of unknown risk highlights ethical issues regarding proxy consent for pediatric participation. It has also been difficult to conduct appropriate pharmacokinetic and pharmacodynamic pediatric dose-finding studies for NOAC. Because of the central role of platelets in arterial thrombosis, 3 antplatelet therapy is potentially important but there are few definitive studies of these drugs in children.4 The currently FDA-approved antiplatelet drugs are listed in the Table.5 The different baseline biology of platelets in neonates and children compared to adults demonstrates the need for specific study of antiplatelet agents in children.6 Summary: A body of evidence has accumulated over many years for the use of heparin and warfarin anticoagulation in children.1 Although NOAC have been successfully introduced in adult patients, these drugs cannot yet be recommended in pediatric patients because of the current lack of data in children.

| S18 | Saturday, November 1, 11:35-11:55; Hall B | ANTIPHOSPHOLIPID SYNDROME IN CHILDREN - SHOULD SIMILAR DIAGNOSTIC CRITERIA BE APPLIED? – YES | Vittorio Pengo | Clinical Cardiology, Thrombosis Center, University of Padova, Italy

According to the revised classification criteria, Antiphospholipid Antibody Syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met. Clinical criteria comprise objectively proven venous or arterial thrombosis and pregnancy morbidity (fetal death, premature birth, multiple early abortions). Laboratory criteria include coagulation tests to detect the presence of Lupus Anticoagulant (LA) and two enzyme-linked immunosorbent assays (ELISA) to measure autoantibodies directed against cardiolipin (aCL ELISA) and B2-Glycoprotein I (β2GPI ELISA). Positive laboratory tests must be confirmed on two or more occasions at least 12 weeks apart. Patients with more than one positive laboratory test are placed in classification category I, while those with a single positive test are placed in classification category II. Moreover, two other subgroups of APS patients should be acknowledged depending on the presence or absence of additional risk factors for thrombosis. In 1990, we described the case of a 13 year old girl with renal artery thrombosis and hypertension. A cerebrovascular accident and a probable occlusion of the superior mesenteric artery also occurred. Of note one month before the patients suffered of acute gastroenteritis. Very high levels of ‘lupus anticoagulant’, anticardiolipin antibodies as well as false positive Venereal Disease Research Laboratory tests were strongly positive. Nowadays, it is well recognized that there is a strong association between thrombosis and a full positive aPL profile (triple positivity). Usually LA potency is strong in these patients and the titer of aCL (mostly IgG) and β2GPI is high. In this case a high recurrence rate of thrombosis and pregnancy loss, despite antithrombotic treatment, is observed. When IgG aβ2-glycoprotein I and IgG β2-glycoprotein I-Domain I and results showed that both were strongly positive. Nowadays, it is well recognized that there is a strong association between thrombosis and a full positive aPL profile (triple positivity). Usually LA potency is strong in these patients and the titer of aCL (mostly IgG) and β2GPI is high. In this case a high recurrence rate of thrombosis and pregnancy loss, despite antithrombotic treatment, is observed. When IgG aβ2GPI are affinity purified from plasma of these patients they show a high LA activity when spiked with normal plasma. Moreover, affinity purified IgG aβ2GPI show marked positivity when tested in aCL ELISA. Thus, antibodies to β2GPI affinity purified from plasma of these patients reproduce the positivity of all the three tests found in the original plasma. Therefore, according to Witebsky’s postulates, triple positive patients with primary APS resemble a true autoimmune disease as the antibody (aβ2GPI) is
identified, the corresponding Ag is known and an analogous response causes a similar disease in experimental animals. The pathogenic α2GPI when present in sufficient amount causes vascular thrombosis in a way that is not fully understood. On the other end when a single positive test is present the association with thrombosis is weak or absent. In newborn or children a α2GPI antibodies may be the only positive test and when tested for specific Domain they are not directed to domain I and thus not associated to thromboembolic events.

S19
Saturday, November 1, 17:00-17:20; Hall A
PRIMARY PREVENTION OF CORONARY ARTERY DISEASE BY ASPIRIN - YES, BECAUSE OF OTHER POTENTIAL BENEFITS
Carlo Patrono
Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

As with other cardiovascular prevention strategies (i.e., blood pressure or lipid lowering), low-dose aspirin can only reduce a fraction (about one quarter) of all major vascular events, not because of “resistance” to its antiplatelet effect, but because of the multifactorial nature of atherothrombosis.1 As with statins or anti-hypertensive drugs, the absolute benefits of aspirin (how many vascular events can be prevented by treating 1,000 patients for one year) are linearly related to the underlying cardiovascular risk of the patients.2 Thus, its benefit/risk profile can vary substantially over the underlying cardiovascular risk continuum, from an area of high risk where benefits clearly outweigh the excess of major bleeding complications to an area of low risk where the number of vascular events avoided equals the number of major bleeds caused by aspirin. While the evidence from randomized clinical trials in these areas of the cardiovascular risk continuum is pretty straightforward and forms the basis of current treatment guidelines and recommendations, there is an area of intermediate risk where we clearly need new trials. At least 4 are currently ongoing in about 50,000 subjects considered to be at enhanced cardiovascular risk because of diabetes mellitus (ASCEND and ACCEPT-D), advanced age (ASPREE) or a cluster of risk factors that do not include diabetes (ARRIVE).3 Finally, there is a very large body of evidence suggesting that aspirin may interfere with the early stages of neoplastic transformation of a normal intestinal epithelium (particularly, in the colo-rectal section) towards a sporadic adenoma and, perhaps, its progression to cancer.4 It has been argued that even a 10% reduction in overall cancer incidence from prophylactic aspirin treatment would tilt the balance of benefits and risks, and substantially broaden the indication for treatment in populations at average risk.4 Following the successful paradigm of the development of low-dose aspirin as an antithrombotic agent, additional joint efforts of Academia and Industry are urgently needed in order to understand its mechanism of action as a chemopreventive agent, define the optimal dose and dosing regimen to achieve this effect, and demonstrate its efficacy and safety in this setting.

References:

S20
Saturday, November 1, 16:20-16:40; Hall B
PLASMA DERIVED VERSUS RECOMBINANT FACTOR VIII CONCENTRATES: WHICH ONE TO CHOOSE? - IN FAVOR OF RECOMBINANT PRODUCTS
Paul Giangrande
Oxford Hemophilia & Thrombosis Centre, Oxford University Hospitals NHS Trust (UK)

Safety with regard to transmission of pathogens is of prime concern in the selection of products for the treatment of hemophilia. The introduction of heat-treatment and solvent/detergent treatment in the mid-1980s effectively eliminated the risk of transmission of HIV and HCV (hepatitis C) through the use of plasma-derived products. However, outbreaks of hepatitis A in several countries in the early 1990s served to remind us that such virucidal methods cannot be relied on to protect patients against all viruses. The periodic identification of new blood borne pathogen such as avian influenza, West Nile virus and SARS inevitably heightens anxiety in the haemophilia community. Parvovirus B19 may still be transmitted by administration of modern plasma-derived concentrates subjected to heat treatment at 100 °C or even a combination of heat and solvent/detergent treatment. Even though infection with parvovirus is of little significance in normal subjects, this again demonstrates that no current viral inactivation process will entirely eliminate the risk of transmission of conventional viruses. Reassurance from experts that the risk of prion transmission and vCJD from plasma-derived products used to treat patients with hemophilia appears remote is welcome but no-one has yet dared to venture that there is absolutely no risk. In view of all the problems associated with viral infections in people with hemophilia over the last two decades, it is clear that there is indeed much wisdom in Aldous Huxley’s aphorism that the lesson of history is that the lessons of history are never learnt. Initial concerns about an increase in the incidence of inhibitors amongst people with hemophilia receiving recombinant products have proved unfounded. Although the results of a randomized trial comparing the incidence in previously untreated patients (PUPs) receiving recombinant with those receiving plasma-derived products are awaited, it would be fair to say that the current consensus is that the incidence of inhibitor development is similar for both types of product. There was certainly no evidence of an increased incidence of inhibitors following the whole-scale switch to recombinant products in countries like Canada and the UK. It is now appreciated that the single most important risk factor for inhibitor development is the underlying molecular defect. There has never been any suggestion that the incidence of inhibitors is increased in patients with hemophilia B receiving recombinant factor IX. The price of recombinant products has fallen sharply in many countries over the last few years. Recombinant products are now cheaper than plasma products in the UK, following a national tender for procurement.

Recombinant products are the structural backbone of all novel products under hemophilia care, such as the various long-acting factor VIII and IX preparations. A blanket refusal to adopt recombinant products would threaten the very future of hemophilia care. By switching to conventional or novel recombinant products, we are helping to secure effective and safe treatment for people in developing countries. The World Federation of Hemophilia estimates that two-thirds of the
people with hemophilia in the world receive little or no treatment for their condition. As patients in more affluent parts of the world as North America, Europe and Australia and Japan convert inexorably to recombinant products, manufacturers of plasma-derived products there will be forced to seek new markets in the developing world and these will also have to be competitively priced. Ultimately, it should be patients who decide which class of treatment they receive. In my experience, the vast majority will express a preference for recombinant products over plasma-derived ones if offered a choice. Whilst product safety is undoubtedly the main consideration, convenience is also another issue (greater solubility, smaller volume of reconstitution and better mixing devices).

S21
Friday, October 31, 14:40-15:00; Hall A
INDIVIDUALIZED PROPHYLAXIS REGIMENS
Elena Santagostino
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Prophylaxis is the standard of care for children with severe hemophilia in order to prevent joint damage and crippling that represent the most serious long-term complications of the natural history of the disease. Although widely used with success since late ‘70s, no standard prophylaxis regimen is applied universally. Given similar efficacy, low-dose regimens may be more convenient especially in children. In fact, despite undeniable advantages, there are several barriers that stand in the way of the implementation of primary prophylaxis as for instance the need for an adequate and stable venous access and the non-negligible costs related to factor consumption on the long term. Moreover a direct comparison between the Dutch and the Swedish cohort, representing the epitome of low- and high-dose prophylaxis, was done to understand if there is a gain in using high-dose regimens (1). This study showed a small incremental benefit in all outcome parameters including joint status and joint bleeding rate, with the exception of quality of life. However it was underlined that such difference could not be attributable only to the dosing regimen but also to the age at prophylaxis onset that was younger in the Swedish cohort. On the other hand, at individual level, data on orthopedic outcome suggest that there is a proportion of patients that can maintain a normal joint status by using low-dose regimens. In this light, treatment individualization is the keyword of prophylaxis accomplishment. Indeed, the use of incremental schedules of prophylactic infusions is of some value since it tailors treatment on the basis of the bleeding phenotype and allows to start with few infusions (1-2) per week. This was the strategy used to design the Canadian Hemophilia Primary Prophylaxis (CHPS) study where treatment started with once weekly infusions and escalated to twice-weekly or alternate day if the bleeding pattern met certain criteria. After 5 years of follow-up, 40% of subjects were still on once weekly prophylaxis, 32% were on twice weekly prophylaxis, and 28% on alternate day’s regimen (2). The benefit in terms of joint outcome provided by the standard regimen was little and although there was sufficient evidence to prefer either prophylactic regimen over on demand treatment, a trial comparing the two prophylactic regimens is warranted in order to ascertain long-term outcome differences.

References
Problem Statement: Ambulatory cancer patients have an increased risk of venous thromboembolism (VTE), which is maximal in patients receiving chemotherapy, particularly antiangiogenic agents. Among the mechanisms invoked to explain this association there is a disturbance of vascular homeostasis consequent to the inhibition of vascular endothelial growth factor (VEGF). Genetic polymorphisms could regulate VEGF-A production. However, the relationship between VEGFA gene variants and VTE isn’t clarified. This study aimed at investigating the predictive role of VEGFA gene promoter SNPs for a first VTE episode in cancer out-patients treated with chemotherapy.

Method: VEGFA -1540A/C, -1512 18bp Ins/del, -1451T/C, -116G/A and +405 G/C gene promoter polymorphisms were retrospectively evaluated in 437 subjects, including 140 controls and 297 patients with histologically diagnosed cancers. All patients had to be at the start of a new chemotherapy regimen (2% neoadjuvant, 35% adjuvant and 63% metastatic treatment); 23% of patients received concurrent bevacizumab. The study outcome was defined as the occurrence of a first symptomatic or asymptomatic VTE episode, either deep venous thrombosis (DVT) or pulmonary embolism (PE), during active treatment.

Results: Both groups were in Hardy-Weinberg equilibrium and no difference was observed between patients and control subjects. VTE occurred in 9% (8 PE and 18 DVT) of cancer patients (median TTE: 3.4 months). In particular 11 (6 non-fatal sub-segmental PE and 5 DVT) patients had incidental VTE at time of CT-scan for restaging. SNPs analysis of observed allele and genotype frequencies showed a significant association in a dominant inheritance model of the VEGFA -116A allele (OR= 0.26; p=0.0034) in cancer patients who remained VTE-free during chemotherapy. Moreover, VEGFA -460 GC genotype was significantly associated with VTE incidence during chemotherapy in an over-dominant inheritance model (OR= 2.86; p=0.016). Of interest, 21 (13%) of 162 cancer patients carrying the VEGFA -116GG genotype developed VTE compared to 5 (5%) and none of 107 and 28 patients carrying the -116GA and -116AA genotypes, respectively (p=0.004). Multivariate Cox proportional hazards survival analysis confirmed the association found in the SNPs analysis, being the VEGFA -116 A allele significantly associated with a decreased risk of VTE with a HR of 0.21 (95% C.I.: 0.07–0.58; p=0.003). These findings were substantially unmodified in a subgroup analysis of bevacizumab-treated patients (n=69), in whom the VEGFA -116A allele confirmed to be protective for VTE in a dominant inheritance model (OR= 0.09; p=0.005) with a 0.12 HR (95%C.I.: 0.02 – 0.89; p=0.039) at Cox analysis. Finally, 18 (26%) patients developed hypertension as a bevacizumab-adverse event. Among these, only one patient carrying the VEGFA -116GA genotype developed concurrent VTE during bevacizumab administration. Conclusion: These results suggest that VEGFA might represent a candidate gene contributing to VTE pathogenesis in chemotherapy treated cancer patients and suggest that VTE risk during chemotherapy might be genetically identified. Validation studies are needed for translation into clinical practice. Partially supported by PO FESR 2007/2013 Linee di Intervento 4.1.1.1 - SIASOP.

Disclosure of Interest: None Declared

OO2
Friday, October 31, 12:40-13:00; Hall A
COAGULATION RESONANCE AMPLITUDE (CORA) TECHNOLOGY PROVIDES A NOVEL VISCOELASTIC ASSESSMENT OF SIMULTANEOUS COAGULATION COMPONENT ANALYSIS
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Problem Statement: Improved understanding of the cell based model of homeostasis and current enthusiasm for viscoelastic technology (VET) have advanced our ability to diagnose, monitor, and treat perturbations of post injury coagulation. Despite this progress, several challenges appear to have limited widespread adoption of VET. These include environmental sensitivity to vibration/contact, labor intensive titration, inability to generate multiple, simultaneous results, and difficult standardization of instrumentation. We theorized that the new CORA® VET would provide equivalent results to the TEG 5000 system but with amelioration of the challenges described, resulting in a simplified, more efficient and user friendly technology.

Method: 300 whole blood samples from three sites were split and analyzed on both the TEG 5000 and the new CORA instrument. The CORA system produces the same numeric results in the familiar TEG parameters and units, but incorporates analysis of clot viscoelastics via a series of non-contact measurements of resonance frequency in response to controlled external vibration, providing a direct measure of clot stiffness. The system uses a disposable microfluidics cartridge, which automates sample preparation, provides electronic quality control, reduces required blood sample volume, and enables simultaneous running of multiple separate assays on the same whole blood sample.

Results: Correlation coefficient r values of the split sample analysis for the R and MA parameters comparing CORA and TEG 5000 were 0.98 and 0.99, respectively with CORA results being produced in four simultaneous channels [citrated RapidTEG® (RT), Kaolin (K), Kaolin+Heparinase (KH), and Functional Fibrinogen (FF) assays].
Conclusion: This initial pilot study suggests that the CORA VET generates comparable results to the TEG 5000 system, but with amelioration of many current challenges of VET. An important advantage is the added ability to run simultaneous RT, K, KH, and FF assays. While further study is indicated, these results suggest that the CORA will likely improve our ability to diagnose, monitor, and treat post injury coagulation disorders.

Disclosure of Interest: None Declared

O03
Friday, October 31, 12:50-13:00; Hall B
CLINICAL AND LABORATORY CHARACTERISTICS OF CHILDREN WITH VENOUS THROMBOEMBOLISM AND PROTEIN C DEFICIENCY: AN OBSERVATIONAL ISRAELI-GERMAN COHORT STUDY
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Problem Statement: Venous thromboembolism [TE] is a multifactorial disease and protein C deficiency [PCD] constitutes a major risk factor. In the present study the prevalence of PCD and the clinical presentation at TE onset including neonatal purpura fulminans in a cohort of children are reported.

Method: In 367 unselected children (0.1-19 years) recruited between July 1996 and December 2013, a comprehensive thrombophilia screening was performed along with recording of anamnestic data.

Results: Twenty-five of 338 children (7.4%) had protein C deficiency [PCD]. Mean age at first TE onset was 10 years (range 0.1 to 18). Leading thromboembolic manifestations were neonatal purpura fulminans (n=5), TE of cerebral veins (n=3), stroke (n=2) deep veins (DVT) of the leg (n=10), DVT & pulmonary embolism (n=2) and DVT & pelvic veins (n=3). In 12 patients concomitant risk factors for TE were identified, whereas 13 children developed TE spontaneously. A positive family history of DVT was found in 10 children.

Conclusion: In this unselected cohort of pediatric patients with symptomatic TE the overall prevalence of protein C deficiency [PCD] was 7.4% with 1.5% presenting with neonatal purpura fulminans. Given its clinical implication for patients and family members, thrombophilia testing should be performed and the benefit of medical or educational interventions should be evaluated in this high risk population.

Disclosure of Interest: None Declared

O04
Friday, October 31, 18:10-18:20; Hall A
AMYLOID PEPTIDE-DEPENDENT ACTIVATION OF HUMAN PLATELETS: ESSENTIAL ROLE FOR Ca2+ AND ADP
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Problem Statement: Alzheimer’s disease is associated with the accumulation of amyloid β (Aβ) peptides in the brain. Besides their cytotoxic effect on neurons, Aβ peptides are thought to be responsible for the atherothrombotic complications associated with Alzheimer’s disease, which are collectively known as cerebrovascular disease.

Method: Platelet aggregation, thrombus formation in whole blood under flow conditions, calcium imaging and classical biochemistry were utilized to investigate the effect of Aβ peptides on human platelets.

Results: We discovered that the 25-35 domain of Aβ peptides induce an increase in platelet intracellular Ca2+ that stimulates α- and dense granule secretion and leads to the release of the secondary agonist ADP. Released ADP acts in an autocrine manner as a stimulant for critical signaling pathways leading to the activation of platelets. This includes the activation of the protein kinases Syk, protein kinase C, Akt, and mitogen-activated protein kinases. Ca2+-dependent release of ADP is also the main component of the activation of the small GTPase Rap1b and the fibrinogen receptor integrin αIIbβ3, which leads to increased platelet aggregation and increased thrombus formation in human whole blood.

Conclusion: Our discoveries complement existing understanding of cerebrovascular dementia and suggest that Aβ peptides can induce vascular complications of Alzheimer’s disease.
Problem Statement: NADPH oxidases (NOXs) contribute to platelet activation by a largely unknown mechanism. Here, we studied the effect of the novel NOX inhibitor 2-acetylphenotiazine (2-APT) on human platelet functional responses and intracellular signaling pathways.

Method: The generation of superoxide ions was assessed by single cell imaging on adhering platelets using dihydroethidium (DHE), while other reactive oxygen species (ROS) were detected with 5-((and-6)-carboxy-2,7'-dichlorodihydrofluorescein diacetate (CM-H2DCFDA). Whole blood thrombus formation, washed platelet aggregation, integrin αIIbβ3 inside-out signaling, Syk phosphorylation, and protein kinase C (PKC) activation were analyzed to understand the functional consequences of NOX inhibition by 2-APT in platelets.

Results: Superoxide ion generation stimulated by platelet adhesion on collagen and fibrinogen was significantly inhibited by 2-APT in concentration-dependent manner (IC50 = 306 nM and 227 nM, respectively), whereas cumulative ROS accumulation was not affected by this pharmacological agent. 2-APT also abolished collagen-dependent whole blood thrombus formation and washed platelet aggregation in response to collagen but not thrombin. The activation of integrin αIIbβ3 and protein kinase C in response to the GPVI-specific agonist collagen-related peptide (CRP) resulted significantly reduced, whereas the same responses to thrombin were not significantly affected by 2-APT. Finally, Syk activation in response to collagen but not thrombin was inhibited by 2-APT.

Conclusion: Taken together, our results suggest that 2-APT attenuates GPVI-specific signaling and is a novel inhibitor of collagen-induced platelet responses. Therefore, NOXs can represent a novel anti-thrombotic drug discovery target.
Problem Statement: Extracellular fibrinogen binding protein (Efb) from Staphylococcus aureus inhibits platelet activation and impairs homeostasis in vivo. We aimed to clarify the mechanism of action of Efb and to verify previous claims that interference with fibrinogen binding is the molecular mechanism underlying the antiplatelet activity of Efb.

Method: We assessed the antiplatelet activity of full length Efb, Efb N-terminal domain (Efb-N) and Efb C-terminal domain (Efb-C) using aggregation experiments in human plasma and thrombus formation assays in whole human blood under physiological shear stress conditions. We also assessed fibrinogen or Efb/Efb-N/Efb-C binding to platelets by flow cytometry.

Results: Both full length Efb and Efb-N strongly inhibited platelet aggregation and thrombus formation, whereas Efb-C did not. Surprisingly, the ability of platelets to bind fibrinogen was increased instead of inhibited by Efb and Efb-N both in resting and thrombin-stimulated conditions. Efb and Efb-N were also shown to interact with resting platelets in the presence of fibrinogen, with platelet stimulation by thrombin decreasing rather than increasing the interaction with Efb and Efb-N.

Conclusion: The N-terminal domain of Efb strongly inhibits platelet activation by a novel and unexpected mechanism that does not involve interference with fibrinogen binding. Fibrinogen is actually necessary for Efb to bind and inhibit platelets. Our observations warrant a revision of our understanding of the mechanism of action of Efb as an antiplatelet agent and suggest that Efb should be investigated further for the development of a novel antithrombotic treatment.

Disclosure of Interest: None Declared

O08
Saturday, November 1, 12:10-12:30; Hall A
CATHETER DIRECTED THROMBOLYSIS ALONG WITH MECHANICAL THROMBOSAPIRATION IN THE MANAGEMENT OF PROXIMAL LOWER LIMB DEEP VENOUS THROMBOSIS- A PROSPECTIVE STUDY WITH 6-MONTH FOLLOW-UP.
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Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences & Research, Bangalore, India

Problem Statement: Catheter-directed thrombolysis (CDT) with assisted mechanical thrombolysis is now becoming the standard of medical care for proximal deep vein thrombosis (DVT). We studied the immediate and intermediate (six months) safety and effectiveness of CDT in patients with proximal lower limb DVT.

Method: Thirty consecutive patients aged between 20-70 years with proximal lower limb DVT formed the study group. CDT was done using streptokinase infusion. Un-fractionated heparin (UFH) was given along with streptokinase. Mechanical thrombectomy was performed in addition to thrombolytic therapy. After 6 months, post-thrombotic syndrome (PTS) and deep venous patency were assessed by using Villalta scale and duplex ultrasound, respectively.

Results: Thirty patients with proximal lower limb DVT were treated with CDT. Mean age of the study patients was 41.7 +/- 15 years. Mean duration of illness was 13.3 +/- 12 days. The mean duration of thrombolysis was 4.5 +/- 1.3 days. Grade III (complete) lysis was achieved in 10 (33%) and grade II (50%–90%) lysis in 20 (67%) of patients. Patients with significant residual lesion in grade II lysis following CDT underwent percutaneous transluminal angioplasty alone (12/20) or venous stenting (8/20). Four patients (13%) developed pulmonary embolism following CDT and among them 2 (6.5%) patients died. Eleven patients (37%) had minor bleeding or hematoma at local site, and 7 (23%) developed anemia requiring blood transfusion and 4 (13%) patients had thrombocytopenia. After 6 months, iliofemoral patency was found in 20 (72%) and PTS was seen in 6 (21%) patients. Two (6.5%) patients died during follow-up due to nephrotic syndrome and carcinoma breast.

Conclusion: CDT and conventional manual aspiration thrombectomy is an effective treatment for proximal lower extremity DVT with good short and intermediate outcome.

Disclosure of Interest: None Declared
(FV Leiden, FV HR2, FII G20210A, β-fibrinogen-455G>A, FXIII-A Val34Leu, PAI-1 4G/5G), homocysteine metabolism (MTHFR C677T, MTHFR A1298C) intermediate risk factors (ACE I/D, apoE ε2-ε4) was performed by using a multilocus genotyping assay (CVD Strip Assay, ViennaLab, Austria) and for human platelet alloantigens (HPA-1, -2, -3 and -5) by ASO-PCR with sequence-specific primers according to Klüter et al. (Vox Sang 1996; 71: 121-5).

Results: Among investigated polymorphisms, we have found a strong association between the presence of FV Leiden and PAIS (OR=8.29; 95% CI=1.95-35.24, P=0.004). Furthermore a 2.89-fold increased risk for PAIS was found in carriers of the ACE I/D genotype (95% CI=1.05-7.93; P=0.038), whereas the presence of at least one HPA-3b allele was associated with more than a 2-fold lower risk for the development of PAIS (OR=0.39; 95% CI=0.18-0.86, P=0.020). The presence of combined heterozygosity for FV Leiden and FV HR2 (2 out of 7 heterozygotes for FV Leiden) was identified in children with PAIS only. Moreover a 5.51-fold increased risk for PAIS (95% CI=1.22-24.82) was observed in children with the genotype combination GA (FV Leiden) and AA (wild type FV HR2).

Conclusion: As this study has clearly demonstrated the role of inherited thrombophilia in the pathogenesis of PAIS we strongly support inherited thrombophilia testing. However, by performing the first-line thrombophilia screening, including FV Leiden, FII G20210A and MTHFR C677T, we would be able only to identify the strongest association between FV Leiden and PAIS as FII G20210A and MTHFR C677T were not found to be associated with PAIS in Croatian children. The extended inherited thrombophilia-testing panel has enabled us to identify new polymorphisms associated with PAIS and combined genetic traits that have to be confirmed in other population studies.

Disclosure of Interest: None Declared

O10 Saturday, November 1, 15:10-15:30; Hall A STRATEGIC MANAGEMENT PLAN TO SUCCESSFULLY IMPLEMENT NEW ORAL ANTICOAGULANTS (NOAS) IN ANTICOAGULATED PATIENTS 2010-2014
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Problem Statement: After many years of medical research the arrival of the NOAs has initiated a new era in the treatment and prevention of thromboembolic risk in patients with non-valvular atrial fibrillation (NVAF). The NOAs have represented a challenge for its implementation in Health Centers around the world mainly due to the absence of a Strategic Management Plan to implement the follow-up of patients with NOAs. In 2010 at the CCSJ we confronted this need by quickly adapting the Hemostasis and Stroke Medical Unit, reason why we have created the following protocol for the NOAs treatment.

OBJECTIVES: 1-Adapting our Central Database and extracting patients prescribed with NOAs. 2- Follow-up the adherence as well as the potential side effects during the treatment and providing advice before patients’ surgery. 3- Defining a protocol for the integration of the work of the different medical teams being the Anticoagulation Unit as the Management.

Method: Since November 2011 until May 2014 we have carried out 58.862 controls of Oral Anticoagulant (OAs) to 1.815 patients. Out of those 1.815 patients, 907 were diagnosed NVFA, men 562 (62%), women 345 (38%). Average age was 75 years old (age ranging from 18 to 97). From those 907 patients we started the prescription of Dabigatran in 348 patients (38.3%), 216 of which were men and 132 women. In 2012 and 2013 we incorporated a total of 79 more patients to our Database and prescribed them Rivaroxaban and Apixaban, results from these two NOAs are still pending analysis.

We created an outpatient visit schema where we assessed the following: cardiologic report, age, weight as well as CHA2 DS2-VASC and HAS-BLED score. We decided to use the same Database of patients that were prescribed with traditional OAs and then assigned them a new ID the NOAs patients.

Inclusion Criteria: Patients with (NVAF).

Exclusion Criteria: Patients with digestive and brain haemorrhage, kidney malfunction and patients with valvular prostheses. During the 1st year the appointments were every 4, 8 and 12 weeks. From the 2nd year onwards every 16 weeks.

Results: During our research we have not seen any bleeding complications nor any embolic-stroke that may have require any emergency treatment.

RESULTS: Analysis of data from 348 patients treated with Dabigatran.
N=348
Adherence 336 96.6% Family stress, Epigastralgia 5 1.4 % Medicine intake without breakfast or dinner, Itch 2 0.6 % Forearm-scalp,Minor bleeding 3 0.8 % Epistaxis - gingivorrhagia
Anaemia 1 0.3 % Colon Polyps,Dyspnoea 1 0.3 % Intracavitary diagnostic * Intracavitary thrombus: Inconsistent medicine intake due to a trip India.

Conclusion: 1-The use of a Central Database in our Anticoagulation Unit allowed us to have a unique record of all the patients treated by CCSJ. 2-The out visit patient schema allowed us to assess and study the adherence as well as any side effects to NOAs treatment. The periodic patient visits (3-4 times per year) are highly recommended since they contributed to better diagnose others hematologic pathologies in the multi pathology cardiovascular patients. 3- The task of the Hematologist and the Anticoagulation Units ought to play a leading role in the follow-up and management of these patients.

Disclosure of Interest: None Declared

O11 Saturday, November 1, 17:30-17:45; Hall B 3-YEAR RESULTS FROM SPINART: PROLONGED REDUCTION OF BLEEDING WITH PROPHYLAXIS USING BAYER’S SUCROSE-FORMULATED RECOMBINANT FACTOR VIII

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Problem Statement: The benefits of primary prophylaxis in preventing joint damage in pediatric patients with severe hemophilia A have previously been established; however, prospective data on long-term outcomes of prophylaxis are
lacking in adults with hemophilia A. In the 3-year SPINART study, routine prophylaxis and on-demand treatment were compared in adults with severe hemophilia A. We report final SPINART efficacy and safety results after 3 study years. Method: The open-label, randomized, controlled, parallel-group, multinational SPINART study enrolled males aged 12–50 years with severe hemophilia A who had ≥150 exposure days with any factor VIII (FVIII) product, no inhibitors, no prophylaxis for >12 consecutive months in the past 5 years, and 6–24 documented bleeding events or treatments in the previous 6 months. All patients were treated with Bayer’s succrose-formulated recombinant FVIII (rFVIII-FS), either on demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation by 5 IU/kg permitted once per year). The primary efficacy endpoint, bleeding frequency (number of all bleeding episodes) at 1 year, has been previously reported. Endpoints reported here are total and annualized numbers of all bleeding episodes, joint bleeding episodes, spontaneous bleeding episodes, and trauma-related bleeding episodes. Between-group comparisons of bleeding frequency were made within the framework of a negative binomial regression model to account for different follow-up times of patients who discontinued prematurely, with stratification variables (presence of target joints at baseline, number of previous bleeding episodes at baseline) included in the model. Safety variables included adverse events (AEs), serious AEs, and inhibitor development. Results: 84 patients (42 prophylaxis, 42 on demand) comprised the intent-to-treat population. The total number of all bleeding episodes during the 3-year study was significantly lower with prophylaxis versus on demand (median, 2.0 vs 96.5, respectively; P<0.0001). Annualized number of all bleeding episodes (median [quartile 1; quartile 3], 0.7 [0; 1.6] vs 37.4 [24.1; 52.6]), total joint bleeding episodes (median, 1.0 vs 67.0), and joint bleeding episodes per year (median, 0.3 vs 27.3) were all lower with prophylaxis versus on demand. The numbers of spontaneous and trauma-related bleeding episodes were also lower with prophylaxis versus on demand. Observed AEs were consistent with the established rFVIII-FS safety profile. No patient developed inhibitors. Conclusion: Long-term prophylaxis with Bayer’s rFVIII-FS is efficacious in decreasing bleeding episodes, including joint bleeding episodes, in adults with severe hemophilia A. 75% of prophylaxis patients had <2 bleeding episodes per year during the 3-year study. No inhibitors were reported.

Disclosure of Interest: M. Manco-Johnson Speakers Bureau of: Has been an advisory board participant for Bayer, C. Kempton Consultant for: Bayer, M. Reding Grant / Research Support from: Received clinical trial support from Bayer, Baxter, Biogen Idec, Octapharma, Nova Nordisk, and Pfizer, Consultant for: Bayer, Baxter, Biogen Idec, Octapharma, Nova Nordisk, and Pfizer, Speaker Bureau of: Advisory board member or speaker for Bayer, Baxter, Biogen Idec, Octapharma, Nova Nordisk, and Pfizer, S. Gorano v: None Declared, L. Gercheva: None Declared, L. Rusen: None Declared, V. Uscatescu: None Declared, M. Pierdominici: None Declared, D. Walker Employee of: Bayer HealthCare Pharmaceuticals, W. Hong Employee of: Bayer HealthCare Pharmaceuticals

O12 Saturday, November 1, 17:45-18:00; Hall B EFFICACY OF PROPHYLAXIS USING A PHENOTYPE-GUIDED DOSING STRATEGY WITH BAY 94-9027: RESULTS OF A PHASE 2/3 MULTICENTER, PARTIALLY RANDOMIZED, OPEN-LABEL TRIAL (PROTECT VIII) Mark Reding1, Jerry Powell2, Elena Santagostino2, Heng Joo Ng3, Mel Lederman3, Maria Wang4, René Walsch5, Mirjam Sax4, Lisa A. Michaels5 and on behalf of the investigators of the PROTECT-VIII Trial 1University of Minnesota Medical Centre, Minneapolis, MN, 2University of California, Davis, Sacramento, CA, United States, 3Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy, 4Department of Hematology, Singapore General Hospital, Singapore, Singapore, 5Bayer HealthCare Pharmaceuticals, Whippany, NJ, United States, 6Bayer Vital GmbH, Leverkusen, 7Bayer Pharma AG, Berlin, Germany

Problem Statement: Prophylactic infusion with factor VIII (FVIII) has beneficial effects for joint arthropathy in patients with severe hemophilia A. However, the need for frequent intravenous infusions creates barriers to patient compliance and makes adherence to prophylaxis difficult. BAY 94-9027 is a site-specific PEGylated FVIII product in clinical development that was demonstrated to have an extended half-life in a phase 1 trial. The longer half-life may allow for longer intervals between treatments, which may therefore improve adherence and allow for tailored prophylaxis based on individual patient bleeding patterns. This study assessed the efficacy of BAY 94-9027 for prophylaxis using different infusion schedules with dosing intervals of up to every 7 days in patients with severe hemophilia A.

Method: This 36-week, phase 2/3, multinational, open-label study enrolled patients aged 12–65 years with severe hemophilia A and ≥150 exposure days to FVIII. Patients were treated on demand or prophylactically with BAY 94-9027 for 36 weeks. Patients using prophylaxis began treatment at 25 IU/kg twice weekly for a 10-week run-in period; observed bleeding during this period was used to determine subsequent dose regimen selection. After 10 weeks, patients with effective prophylaxis (≤1 breakthrough bleed) were randomized 1:1 to 45–60 IU/kg every 5 days or 60 IU/kg every 7 days. Those with ≥2 breakthrough bleeds remained on twice-weekly treatment at higher doses (30–40 IU/kg). Patients in the every-5-days or every-7-days treatment arms could leave their assigned treatment arm and had the option of a one-time change in dose frequency to a more frequent dosing interval if adequate bleeding control was not achieved with higher infusion doses within their treatment arm.

Results: 88% of patients experienced effective prophylaxis and qualified for randomization. All patients assigned to treatment every 5 days (n=43) remained in the treatment arm; 37% of these experienced no bleeds, and median annualized bleeding rate (ABR) was 1.9. 74% of patients assigned to treatment every 7 days (n=43) remained in the treatment arm; 44% experienced no bleeds, and median ABR for all 43 patients in this arm, including noncompleters) was 3.9. For patients (n=32) who stayed in the every-7-days treatment arm (excluding the noncompleters), median ABR was 0.96. The 13 patients who remained in twice-weekly treatment due to ≥2 bleeds during the 10-week run-in period on 25 IU/kg twice weekly reduced their median ABR from 17.4 to 4.1 following higher dosing twice weekly; 15% of these patients
experienced no bleeds. Patients in the on-demand treatment group (n=20) had a median ABR of 23.

Conclusion: This study of treatment with BAY 94-9027 demonstrated the utility of a phenotype-guided dosing strategy for severe hemophilia and showed prevention of bleeding using individualized and less frequent dosing regimens with dose intervals of up to every 7 days.

Problem Statement: Deep vein thrombosis is a medical condition for blood clotting. This is a process for formation of thrombi that either partially or completely block circulation in a deep vein, generally in the lower extremities. Unlike the superficial veins just below the skin surface, the deep veins are surrounded by powerful muscles that contract to force blood back to the heart. One-way valves inside the veins prevent backflow of blood between muscle contractions. The quick and efficient return of blood to the heart using the power of the leg muscles is a crucial phase of the circulatory process. When the rhythm of circulation slows down due to illness, injury, or inactivity, there is a tendency for blood to accumulate or “pool” forming a clot [1, 2].

Method: In this paper, the design, building and testing of an intermittent pneumatic compression device [3] for patients in hospitals who are confined to their beds is presented. The unit can be operated by standard 220 volts AC outlets, which will power the air pumps, or use fluid pressure (compressed air or medical oxygen). Medical Oxygen is available in every hospital room. This will be a considerable development to existing IPC units if implemented in hospitals. The exhaust from these units is simply Oxygen which will be enhance the environment around the patient. Another advantage of using medical Oxygen instead of compressed air generated by a compressor is the low noise of the device. Battery power can also be used in this case instead of the AC power. This modification would reduce the cost per unit and make it available to every bed/patient at reasonable cost. The unit is controlled by a microcontroller, which is programmed to control the valves used in the unit. Five cuffs were used on each leg starting from the ankle and up. Three cuffs were located below the knee and two cuffs above the knee. The lowermost cuff is inflated first on each leg followed by the next higher cuff. When the third cuff is inflated, the first one is deflated and so on. This sequence is repeated till the last cuff (the fifth) is inflated.

Results: There is a training cycle programmed on the microcontroller which will prepare the patient and get him/her to be used to the device the first time the unit is switched on. This training cycle lasts for few minutes after which the standard cycle starts. The source of pressurized air is the Oxygen line which is available in every room in the hospital. Furthermore, work on a less intrusive intermittent pneumatic compression device for the same purpose is underway. The new design should eliminate any discomfort felt by the patient when the classical devices are used.

Conclusion: This arrangement was found to be better than the one-cuff on each leg unit as the blood flow rate increased from the bottom up. This way we guarantee successful performance of the device and eliminate the frequent failures encountered by existing units in hospitals.

Disclosure of Interest: None Declared

PO2
THE ASSOCIATION BETWEEN VENOUS THROMBOEMBOLISM AND LIPID PROFILE
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BACKGROUND AND OBJECTIVE: Lipids and lipoproteins modulate the expression and/or the function of thrombotic, fibrinolytic and rheological factors among patients with cardiovascular disease. Many studies have suggested a link between risk factors of venous thromboembolism (VTE) and dyslipidemia but results are heterogeneous. We sought to identify if dyslipidemia is a risk factor of VTE disease.

PATIENTS AND METHOD: We have developed a hospital-based case-control study was conducted in 32 patients with VTE and 33 age- and gender- matched healthy controls. We were proceeding to compare the lipid profile of the two groups after dosing the total cholesterol, triglycerides, high density lipoprotein cholesterol (c-HDL), low density lipoprotein cholesterol (c-LDL), Lipoprotein Lp (a), Apo-A1, Apo-B and Apo-E. Patients who have cancer and whose take statins or fibrates are excluded.

RESULTS: The two groups have the same demographic characteristics but there were more diabetics, arterial hypertension and obese in the VTE group than the control group respectively (Diabetic: 37% VS18%, hypertension: 68.6% VS 15.2% and (body mass index) BMI ≥30kg/m2: 43.8% VS 18.2%). The mean value of the total cholesterol (CT), the c-LDL, Lipoprotein Lp (a), and Apo-B were statistically Higher in the VTE group compared to control group respectively; CT (4.942±1.409 VS 4.362±0.872mmol/l, P=0.049), c-LDL (3.114±1.100 VS 2.602±0.695mmol/l, P<0.001), Lp (a) (0.205±0.115 VS 0.0819±0.0479 g/l, P <10-3), Apo-B (1.333±0.253 VS 0.8006±0.238 g/l, P<10-3) but there was no statistical significant difference was observed between the two groups in the value of Triglycerides and Apo E respectively (1.710±0.816 VS 1.386±0.636mmol/l, P=0.62), (0.102±0.070 VS 0.0810±0.153 g/l, P=0.48). However, the mean value of c-HDL and Apo-A1 were statically lower in the VTE group; c-HDL (1.048±0.237 VS 1.473±0.334mmol/l, P<0.001) and Apo-A1 (1.010±0.2437 VS 1.414±0.2911g/l, P<10-3). Furthermore, enhanced c-HDL ≤ 0.906 mmol/l was diagnosed in 21 patients (65.6%) in the VTE group versus 4patients (12.1%) in the control group (P< 0.001), so it was also independently associated with a risk of VTE.

CONCLUSIONS: The present study shows a significant association between the occurrence of venous thromboembolism and lower levels of c-HDL and ApoA1 and higher levels of c-LDL, Apo-B and Lp (a), but, there were no effect of Triglycerides and Apo E. Nevertheless, these results must be confirmed with a large population study to prove an eventual independent factor for VTE and dyslipidemia.
Problem Statement: For more than half a century, phenprocoumon and warfarin have been the drugs of choice for long-term anticoagulation, although the use is associated with several problems. After decades of research for alternative, three non-VKA oral anticoagulants (DOACs) are now approved for several indications. Meanwhile there are options for monitoring of the DOACs, although routine monitoring is not necessary. Due to their increasing clinical application it is however also of interest to know their interference with classical haemostaseological point-of-care tests and platelet function tests.

Method: Blood samples from healthy volunteers were spiked with therapeutic and supratherapeutic concentrations of the mentioned selective anticoagulants and investigated with regard to their effects on the following POCTs: activated clotting time (ACT), thromboelastometry with ROTEM®, PFA® and Multiplate®. Light-transmission aggregometry (LTA) with several activators was used also as platelet function assay.

Results: None of these assays showed to be applicable for monitoring of DOACs. At therapeutic concentrations only dabigatran significantly prolonged ACT, whereas all DOACs showed an effect on ROTEM analyses. In contrast, supra therapeutic concentrations of DOACs significantly influenced ACT and ROTEM® analyses. However, even by using whole blood from healthy volunteers, large inter individual variations were observed so that generally more detailed testing is required to confirm such results. LTA measurements revealed only a decrease of the α-thrombin-induced platelet aggregation using dabigatran, but neither dabigatran nor the two DXI showed any influence on PFA® or Multiplate®.

Conclusion: The DOACs dabigatran, rivaroxaban, and apixaban exhibit significant effects on POCTs and platelet function tests, but mostly supratherapeutic concentrations are needed. Although such effects may by rather the exception, it might be wise to additionally perform specific tests for DOACs in the case of unexpected results.

Disclosure of Interest: T. Eller Paid Instructor for: Bristol-Myers Squibb GmbH & Co. KGaA, Bayer Vital GmbH, J. Busse: None Declared, M. Dittrich: None Declared, Tobias Flierder: None Declared, C. Knabbe: None Declared, I. Birschmann Paid Instructor for: Bristol-Myers Squibb GmbH & Co. KGaA

Problem Statement: The International Society of Thrombosis and Hemostasis (ISTH) system of DIC scoring is one of the scoring methods used to diagnose and help manage both patients with overt DIC and those at risk of developing DIC. This study aims to assess the relationship between the ISTH system of DIC scoring and global coagulation test of clot structure, fractal dimension (DF), in patients with sepsis and systemic inflammatory response syndrome (SIRS).

Method: Blood samples were taken from 87 patients with sepsis and SIRS on admission to a large teaching hospital. Citrated and EDTA samples were taken for determination of coagulation parameters (PT, Fibrinogen, D -dimer) and full blood count respectively. ISTH DIC score was determined as defined by Taylor et al., 2001. Rheological analysis was performed on whole unadulterated blood samples to determine Fractal Dimension (DF) of incipient blood clots. Patients were divided into three groups as per ISTH score: Score of 0 = no DIC, ISTH Score > 0 Abnormal Coagulation group, ISTH Score ≥ 5 Overt DIC.

Results: A significant reduction in fractal dimension was observed in the patients with increasing coagulation abnormalities when compared to the group with normal coagulation parameters. DF in the group with normal coagulation parameters was 1.76 ± 0.09, and was 1.71 ± 0.1 and 1.55 ± 0.14 (Mean ± SD) in the abnormal coagulation and overt DIC groups respectively (p < 0.05, One-way ANOVA). Furthermore, DF correlated significantly with ISTH DIC Score (Pearson Correlation Coefficient 0.468, p < 0.001).

Conclusion: Significantly weaker clot microstructure was observed in SIRS and sepsis patients with coagulation abnormalities. Furthermore, patients that exhibited symptoms of overt DIC had significantly weaker clot microstructure than those with coagulation abnormalities but no overt DIC. Abnormal clot microstructure could be associated with failure to form a functional blood clot, leading to the increased bleeding diathesis which is observed in these patients. Further studies are needed to investigate the potential for DF in diagnosis and management of DIC.

Disclosure of Interest: None Declared
P05
CANA RELAPSING INHIBITOR BE PART OF AN OVERACTIVE IMMUNE RESPONSE?
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Problem Statement: Inhibitor development remains the most challenging complication of hemophilia, for both patients and treating physicians. Multiple genetic and environmental factors have been implicated in inhibitor development. The patients’ own immune system obviously plays an important role, although our understanding of the exact immune mechanisms that lead to inhibitor formation have not been completely clarified.

Method: The aim of the present report was to explore the possibility of a relation between a relapsing inhibitor and an overactive immune system.

Results: It involves a 12 year old patient with severe hemophilia who developed an inhibitor at the age of 3 years. He was started on an immune tolerance induction (ITI) regimen with an inhibitor titer of 10BU and at a dosing of 100U/kg/day thrice weekly, using the second generation recombinant product he was receiving when the inhibitor developed. His inhibitor titer fell under 0.5 BU 10 months following ITI initiation and his dosing was gradually reduced to regular prophylaxis program (50U/kg/day thrice weekly). Almost simultaneously, 2.5 years later, a diagnosis of autoimmune thyroiditis and inhibitor relapse was made. A second ITI regimen was started with a pre ITI inhibitor titer of 79 BU and using a plasma-derived product (100U/kg/day thrice weekly. His inhibitor disappeared after 23 months and he was gradually put on a prophylactic regimen using the same plasma-derived product. A few months later an episode of aseptic subcutaneous fasciitis of the right calf was followed. Although his immune laboratory profile failed to reveal anything but the anti-thyroid antibodies, the repeated inhibitor relapses and their simultaneous presentations with the autoimmune/inflammatory episodes argue against mere coincidence.

Conclusion: The immune process in FVIII inhibitor seems to be very complex and many important immunological questions remained unanswered.

Disclosure of Interest: None Declared

P06
INHIBITORS IN HEMOPHILIA: A SINGLE CENTER EXPERIENCE
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Problem Statement: Inhibitor development remains the most serious complication of hemophilia, rendering replacement treatment ineffective. Immune tolerance therapy is to date the only means for inhibitor eradication, however, response to treatment varies widely and is dependent on many factors.

Aim of the present study was to retrospectively report a single pediatric center experience regarding inhibitor development, clinical course and treatment.

Method: Ten severe hemophilia A patients developed an inhibitor out of a total of 50 patients followed at the center (45 hemophilia A, 5 hemophilia B). Data studied included age and intensity of treatment at factor replacement initiation, age of inhibitor diagnosis, exposure days before inhibitor development, mode of treatment (on demand/ prophylaxis), type of factor received (plasma derived/recombinant), factor alternation, family history, IVIS22 mutation presence, immune tolerance induction (ITI) (regimen, duration, CVC placement, additional treatments, response).

Results: Mean age of factor replacement initiation was 1.8 years (1month-4.5 years), with 1/10 patients requiring high intensity dosing due to GI bleeding. Prior to inhibitor development 8/10 patients were on demand treatment and 2/10 were on prophylaxis. No patient was on plasma derived product, while in 2 cases factor alternation was reported. All patients but one of those receiving a single recombinant factor had received a second generation concentrate. In half of the patients exposure days before inhibitor diagnosis were less than 50. Inhibitor titer at diagnosis ranged from 1BU to 70BU (median 14 BU) and maximum titer during course 1.9-2500 BU (median 88 BU). A positive family history for inhibitor development was present in 1/10 patients. Half of the inhibitor patients carried the IVS22 mutation. ITI was offered in 8/10 patients, with a dose ranging from 50U/kg/day thrice weekly to 200U/kg/day at alternating days. In 5/8 patients the recombinant product used at diagnosis was also used for ITI, while in 3/8 patients a plasma derived product was initiated. In all cases bypassing agents (Novoseven, FEIBA) were used for bleeding prevention and treatment during the first months of ITI. A CVC (Hickmann catheter) was placed in 6/8 patients receiving ITI, with 3/6 patients demonstrating catheter related infection, 1/6 catheter related bleeding and 1/6 accidental removal of the catheter. In 2/8 cases ITI is still ongoing whereas in 6/8 cases ITI has been completed, given for 12-48 months. In 3/6 patients ITI was successful, in 1/6 ITI was stopped due to catheter related complications and inability to continue using peripheral veins and in 2/6 ITI was stopped due to inadequate response. Of the 3/6 patients successfully completing ITI 2 have remained inhibitor free and 1 has relapsed. Of the 2/8 patients not receiving ITI one has reached OBU after 15 years of inhibitor presence.

Conclusion: In conclusion, inhibitor presence remains a true challenge for hemophilia patients. Response to ITI, the only curative treatment to date, cannot be guaranteed and is dependent on multiple genetic and environmental factors.

Disclosure of Interest: None Declared

P07
TISSUE FACTOR GENE -603 A/G AND +5466 A/G POLYMORPHISMS ARE NOT ASSOCIATED WITH VENOUS THROMBOEMBOLISM IN CANCER PATIENTS
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Problem Statement: Venous thromboembolism (VTE) is one of the most common complications in cancer patients. VTE is
seen in 15% of cancer patients during the course of their disease. Cancer is related to hypercoagulability due to many factors including activation of clotting system. Several genetic risk factors related to the hemostatic system are known to influence the thrombosis risk. Although factor V Leiden (FVL) is the most common genetic defect causing thrombosis, the impact of gene abnormalities on thrombotic tendency in cancer patients remains poorly explored. Several studies have been focused on the relationship between FVL and VTE with conflicting results. In addition to FVL, other factors related to thrombosis like prothrombin (PT) G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, PAI-1 4G/5G, the promoter region polymorphisms of FVL have been investigated. Tissue factor (TF) is a major physiologic initiator of blood coagulation. However, there is no published data regarding the association of TF gene -603A/G and +5466A>G polymorphisms with VTE in malignancy.

Method: In this study, it is first time these polymorphisms have been investigated in cancer patients with and without VTE. The study was approved by ethical committee. Restriction Fragment Length Polymorphism method was used for the detection of polymorphisms of TF -603A/G in the 5′ upstream region and TF 5466A/G in intron 2 in TF. FVL, PT G20210A and MTHFRC677T polymorphisms were determined by using commercially available Light Cycler kits. The study consists of two groups: cancer patients with VTE were included as group 1 (n=46); group 2 comprises 196 cancer patients without VTE. The genotype and allele frequencies of the polymorphisms between the groups are compared by using chi-square or Fisher exact test, if appropriate.

Results: No differences were observed in the distribution of TF gene -603A/G and +5466A>G genotype frequencies between the groups. Although a slightly increased incidence of +5466 GA genotype in group 1 was seen (17.4% vs. 11.2%), it did not achieve statistical significance. The prevalence of FVL was significantly greater in group 1 compared with group 2 (41.3% vs. 4.1%, p < 0.0001). No differences were also seen in genotypes and allele frequencies of MTHFR C677T and PT G20210A between two groups (p=0.05).

Conclusion: The present study did not show significant association of TF gene -603A/G and +5466A>G polymorphisms with VTE in malignancy, however further larger studies including different ethnic population are needed to confirm our findings.

Disclosure of Interest: None Declared
P10

POLYMORPHISMS RS1800790, RS6046 AND RS5985 AND THEIR ASSOCIATION WITH ISCHEMIC STROKE. A CASE-CONTROL STUDY IN VENEZUELA

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Problem Statement: It is well known that the development of ischemic pathologies may be associated with the presence of multiple factors, where the environmental and genetic factors play an important role. In the present study we evaluate the relationship between the polymorphisms -455 G>A (rs1800790) in β-Fibrinogen gene, R353Q (rs6046) in factor VII (F7) gene and the V35L (rs5985) in factor XII (F13) gene and the risk of ischemic stroke (IS) in a Venezuelan population.

Method: Samples from 73 patients with IS and 100 control subjects were analyzed for the three polymorphisms mentioned above. All polymorphisms were detected by polymerase chain reaction (PCR) followed by enzymatic restriction analysis.

Results: The Odds Ratio (OR) for IS in carriers for the risk allele A for rs1800790 and rs6046 single nucleotide polymorphisms (SNPs) was statistically significant in respect to an increased risk for IS (GG vs. GA+AA: OR= 3.29, 95% CI: 1.58-6.84, p<0.05 and OR= 2.12, 95% CI: 1.10-4.08, p<0.05 respectively). In contrast, when the OR for rs5985 SNP was estimated, a protective effect in the presence of L allele for the polymorphism V35L in F13 was observed (OR=0.76, 95% CI: 0.41-1.40 p<0.05).

Conclusion: A genetic propensity to IS can be attributed to the presence of the risk allele A for the rs1900790 and rs6046 SNPs in the Venezuelan population, suggesting the importance of molecular diagnosis and identification of individual genetic susceptibility in complementing the diagnostic clinician.

Disclosure of Interest: None Declared

P11

THE EFFECT OF LOWER LIMB IMMOBILISATION ON CALF PUMP FUNCTION

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Problem Statement: Orthopedic patients treated with lower limb immobilization are at risk of developing a venous thromboembolism (VTE). We are developing regional and national guide lines to help identify patients treated through Fracture Clinics who should be considered for thromboprophylaxis to reduce this risk. Whilst the mechanism of VTE formation in these patients is poorly understood it is thought that calf pump inactivity and venous stasis play a part.

The degree to which the different types of lower limb immobilization inhibit calf pump activity is unknown. To help us further develop our risk assessment tools, we investigated whether it was possible to activate the calf muscle pump whilst the lower limb was immobilized and how the type of immobilization affected the degree to which it could be activated.

Method: We gained full ethical approval from our institution and local research and ethics committee. Twelve healthy volunteers were recruited. The average age was 27 years (range 18-40), there were 7 males and 5 females.

A Consultant Radiologist used doppler ultrasound to measure peak flow velocity in the Popliteal Vein of the volunteers dominant limb whilst at rest and when performing standardized movements; toe dors flexion, toe plantar flexion, ankle dors flexion, and ankle plantar flexion. The ultrasound scans were performed when the volunteers were not immobilized and when immobilized in a removable fracture support boot (AircastTM), a full below knee synthetic cast through which they could not bear weight, and a full below knee synthetic cast through which they could bear weight.

Results: The peak mean resting Popliteal Vein flow velocities for no immobilization, removable boot, non-weight bearing cast and weight bearing cast were 5.6, 5.2, 4.1, and 4.2 centimeters per second respectively. Comparing each of the immobilization types resting flow with that seen with no immobilization using Students T-test there weren't significant differences (p>0.05). All of the movements in all immobilization types resulted in a significant increase in flow compared to that seen at rest. For all immobilization types the greatest mean peak flow velocities were seen during ankle plantar flexion. The flow rates were 41.0, 44.3, 38.4, 44.4 cm/s respectively. Comparing these means to one another with ANOVA there were no statistically significant differences (p>0.05).
LOW-DOSE RECOMBINANT ACTIVATED FVII IN THE MANAGEMENT OF INTRACTABLE BLEEDING AFTER MAJOR SURGERY: A SINGLE CENTRE EXPERIENCE

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Problem Statement: In the last 15 years, recombinant activated factor VII (rFVIIa) has been frequently used off-label for the treatment of intractable bleeding in various patients without pre-existing hemostatic disorder, including those undergoing surgery. However, there is no definite evidence of its efficacy in the surgical setting and several issues, including risk of thrombotic events and optimal dosing, remain unclear.

The use of reduced rFVIIa doses has been proposed to lower risk of thrombotic events and optimal dosing, remain unclear. The aim of the study was to retrospectively evaluate efficacy and safety of off-label rFVIIa in low (<80 µg/kg) and standard (80-100 µg/kg) doses in the surgical setting (bleeding after major surgery) at a single tertiary care centre (authors' affiliation).

Method: A retrospective analysis (9 years; January 2005 - December 2013) of patients receiving off-label rFVIIa was performed. All patients who fulfilled the criteria (no bleeding disorder with an approved indication for rFVIIa (e.g. acquired or hereditary hemophilia A and B, FVII deficiency, inherited platelet function disorders); rFVIIa given due to the intractable bleeding (defined as a continuous blood loss after the failure of standard hemostatic measurements including surgical intervention, exceeding 1500 ml or at the localization threatening life) related to major surgery; age ≥ 18 years; treatment during the selected time period) were included. Survival, complications, and changes in bleeding, transfusion rate, and selected coagulation parameters were analyzed. Statistical analysis was performed with non-parametric tests; SPSS software was used (version 16; IBM Corp., Armonk, NY, USA), and P < 0.05 was considered significant.

Results: Forty-six patients (27 men; mean age: 59.0 (33-72) years) with 47 bleeding events were identified. Twenty-one patients with 21 bleedings (12 men; 60.7 (41-82) years; group 1) received low-dose rFVIIa (mean dose: 26.3 ± 13.9 (11.7-64.5) µg/kg), whereas 26 patients with 26 bleedings (16 men; 58.5 (21-83) years; group 2) were given a standard dose rFVIIa (92.7 ± 6.8 (82.5-109.0) µg/kg). rFVIIa was given as a bolus in all cases, 11 patients (6 in group 1) received the second dose. The resection of pancreas (10 patients), liver (7 patients), and nephrectomy (5 patients) were the most frequent surgical procedures. No significant differences were observed between the groups in terms of the procedures, localization of hemorrhage, concomitant hemostatic treatment prior and after and transfusion therapy prior the administration of rFVIIa. No significant changes in rFVIIa efficacy (bleeding stopped in 76.2 vs. % 76.9% after the first rFVIIa dose), survival (at 48 hours: 90.4 vs. 80.7%; overall: 80.9 vs. 76.9%), transfusion rate and laboratory parameters were observed between the groups. The rate of complications were low in both groups; only 1 thrombotic event possibly related to rFVIIa was identified in each group.

Conclusion: In the evaluated cohort, lower-than-standard dose of rFVIIa appeared to be comparably effective and safe in controlling the intractable bleeding in adult patients after major surgery. The results have to be interpreted with caution due to the limited number of patients; further analyses are necessary for the definitive evaluation of low-dose rFVIIa in this setting.

Disclosure of Interest: None Declared
demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation of 5 IU/kg permitted once per year). CAJAS assessments were performed at baseline and years 1, 2, and 3. The physiotherapists performing CAJAS assessments were blinded to patient treatment assignment, bleeding history, and previous joint assessment data. Change from baseline to year 3 in CAJAS total score was pre-specified as the second of 2 secondary endpoints; higher CAJAS scores indicate worse joint function. HAEMO-QoL-A was completed at baseline, month 6, and years 1, 2, and 3; higher HAEMO-QoL-A scores indicate better HRQoL. Between-group comparison was made using constrained longitudinal data analysis. Data are presented for the intent-to-treat (ITT) population.

Results: 84 patients (42 prophylaxis, 42 on demand) comprised the ITT population; HAEMO-QoL-A data were available for 41 and 42 patients, respectively. For CAJAS total score, least squares (LS) mean change from baseline to year 3 was 0.63 for on demand and −0.31 for prophylaxis (LS mean difference, −0.94; 95% CI, −1.61 to −0.26; P=0.0072). LS mean change in CAJAS total score for the on-demand and prophylaxis groups was 0.19 and −0.46 at year 1 and 0.34 and −0.57 at year 2, respectively. For HAEMO-QoL-A total score, LS mean change from baseline to year 3 was −6.00 for on demand and 3.98 for prophylaxis (LS mean difference, 9.98; 95% CI, 3.42 to 16.54).

Conclusion: In adults with severe haemophilia A, joint function and HRQoL improved continuously over 3 years with prophylaxis compared with on-demand use.

Disclosure of Interest: W. Hong Employee of: Bayer HealthCare Pharmaceuticals, J. Pocoski Employee of: Bayer HealthCare Pharmaceuticals, D. Raunig Consultant for: Employed by ICON Medical Imaging and is under contract to Bayer HealthCare for work performed for SPINART on the validation of the extended MRI scale and Colorado Adult Joint Assessment Scale. S. Funk Consultant for: Paid consultant on the Bayer-sponsored SPINART study. M. Manco-Johnson Speakers Bureau of: Has been an advisory board participant for Bayer.

P14

JOINT OUTCOMES BY MAGNETIC RESONANCE IMAGING AFTER TREATMENT WITH BAYER’S SUCROSE-FORMULATED RECOMBINANT FACTOR VIII IN THE SPINART STUDY: RESULTS AT THE 3-YEAR EVALUATION TIMEPOINT

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Problem Statement: Long-term prospective data are lacking on the effects of routine prophylaxis on joint outcomes in adults with hemophilia A. Joint status was assessed in the 3-year SPINART study, which compared routine prophylaxis vs on-demand treatment in adults with severe hemophilia A. We report joint outcomes at year 3 obtained using magnetic resonance imaging (MRI).

Method: The open-label, randomized, controlled, parallel-group, multinational SPINART study enrolled males aged 12–50 years with severe hemophilia A who had ≥150 exposure days with any factor VIII (FVIII) product, no inhibitors, no prophylaxis for ≥12 consecutive months in the past 5 years, and 6–24 documented bleeding events or treatments in the previous 6 months. Patients were treated with Bayer’s sucrose-formulated recombinant FVIII (rFVIII-FS), either on demand or as prophylaxis (25 IU/kg 3 times weekly, with dose escalation by 5 IU/kg permitted once per year). MRI was performed at baseline and year 3 to evaluate the structure of 6 index joints. Each MRI was read by 3 radiologists blinded to treatment assignment who independently completed the extended MRI (eMRI) scale; higher eMRI scores indicate greater joint structure damage. The score for each joint was based on the readers’ median change score for each of the 45 eMRI scale items when comparing MRIs from different time points. Total patient score was derived; change from baseline in total patient score was pre-specified as the first in a hierarchy of 2 secondary endpoints. Between-group comparison was made using constrained longitudinal data analysis. Data are presented for the intent-to-treat population.

Results: Of 84 patients enrolled (42 per treatment group), MRI data were available for 38 on-demand and 41 prophylaxis patients. Least squares (LS) mean change from baseline to year 3 on the eMRI scale total score was 0.96 for on demand and 0.79 for prophylaxis (LS mean difference, −0.17; 95% CI, −0.92 to 0.59; P=0.66). LS mean change from baseline to year 3 for on demand and prophylaxis was 0.06 and 0.01 for the eMRI soft-tissue domain (LS mean difference, −0.04; 95% CI, −0.18 to 0.10; P=0.53) and 0.90 and 0.78 for the eMRI osteochondral domain (LS mean difference, −0.12; 95% CI, −0.82 to 0.58; P=0.74).

Conclusion: In adults with severe hemophilia A, progression of structural joint damage was not significantly different between patients using rFVIII prophylactically or on demand over a 3-year follow-up period, although less progression was seen with prophylaxis.

Disclosure of Interest: W. Hong Employee of: Bayer HealthCare Pharmaceuticals, D. Raunig Consultant for: Employed by ICON Medical Imaging and is under contract to Bayer HealthCare for work performed for SPINART on the validation of the eMRI scale and Colorado Adult Joint Assessment Scale. S. Funk Consultant for: Paid consultant on the Bayer-sponsored SPINART study. M. Manco-Johnson Speakers Bureau of: Has been an advisory board participant for Bayer. B. Lundin Consultant for: Is employed by the Centre for Medical Imaging and Physiology at Skåne University Hospital and is under contract to Bayer HealthCare for work performed for SPINART. M. Manco-Johnson Speakers Bureau of: Has been an advisory board participant for Bayer. B. Lundin Consultant for: Is employed by the Centre for Medical Imaging and Physiology at Skåne University Hospital and is under contract to Bayer HealthCare for work performed for SPINART. He has also received reimbursement from Bayer for symposium attendance.

P15

UPPER EXTREMITY DEEP VENOUS THROMBOSIS - PREVALENCE AND RISK FACTORS

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Problem Statement: Studies regarding venous thrombosis of the upper extremity in Romania were not published, at our knowledge, in English speaking literature, possibly due to a lower awareness of the clinician to this diagnosis. The purpose of this presentation is to assess the frequency of upper extremity deep vein thrombosis on patients admitted to the Internal Medicine Department of the Clinical Emergency Bucharest Hospital from January 2012 until June 2014.

Method: Retrospective study conducted on patients admitted to the Clinical Emergency Hospital Bucharest, Romania, between January 2012 and June 2014.

Results: A total number of 22 cases of upper extremity deep vein thrombosis were identified out of a total number of 253
cases with deep vein thrombosis (8.3%). Women were more affected than men (13.9%), and the mean age was 42.8 years. The most affected sites were: subclavian and brachial veins, both with 15 cases (29.4%), followed by the axillary vein, with 11 cases (21.5%). Primary thrombosis was found in more than two thirds of the cases (15 out of 22). Acquired risk factors were malignancies (2 cases), the presence of pacemakers or cardiac resynchronization therapy (2 cases), pregnancy or postpartum period (2 cases), obesity (4 cases). Effort-induced thrombosis was found in two cases. Thrombophilic factors could not be investigated in our hospital and the patients were referred to a tertiary center after treatment completion (usually 3 months). Thoracic outlet syndrome was poorly investigated. The study included only medically ill patients which could explain the absence of catheter related thrombosis. The most frequent method of diagnose was Doppler ultrasonography. Most patients had a computer tomography (18 cases (81.8%)) in order to discover an embolic complication or an occult malignancy. Only one case had associated pulmonary thromboembolism. The most recommended treatment was unfractionated heparin (14 cases, 63.6%), or low molecular weight heparin (7 cases, 31.8%), followed by acenocumarol (19 cases, 86.4%). Novel oral anticoagulants were not prescribed.

Conclusion: The study showed a frequency of upper extremity deep venous thrombosis of 8.3% in accordance with data from the literature.

Disclosure of Interest: None Declared

P16
GENETIC RISK FACTORS ON ATHEROTHROMBOTIC DISEASE: COMPARISON BETWEEN TWO TERRITORIES

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Problem Statement: Atherothrombotic disease is the first cause of mortality worldwide. Myocardial infarction and stroke represent the most important thrombosis complications of arterial thrombosis disease. Between 5 and 10 % of individuals who suffer MI or stroke are 45 years of age or less and it represents a very important health care issue worldwide. Several conditions may contribute to the occurrence of those atherothrombotic diseases in this age group, including environmental and genetic risk factors. The aim of the study was to evaluate the association between the PIA1/A2 polymorphism in the IIIa glycoprotein and C677T polymorphism in the 5, 10 methilnedetetrahidrofolate reductase in patients with myocardial infarction or stroke in two independent case-control studies.

Method: In a case–control study 297 consecutive patients less than 45 years old who had survived their first myocardial infarction were included. The diagnosis of myocardial infarction was based on an electrocardiogram, clinical data and laboratory. They were admitted to the Intensive Coronary Care Unit of the Cardiology Hospital, Centro Médico Nacional Siglo XXI, in Mexico City, Mexico. A total of 297 Mexican subjects without personal history of myocardial infarction, age-gender matched, were included in the control group. In a second independent case–control study, a total of 235 consecutive unrelated patients less than 45 years, with diagnosis of stroke were send them to our research unit and enrolled in the present study. Diagnosis of idiopathic ischemic stroke was considered in all patients after an acute focal neurological deficit with duration greater than 24 h and followed by confirmation by means of brain-computed tomography or magnetic resonance. A total of 235 Mexican subjects without personal history of stroke, age-gender matched, were included in the control group. The PIA1/A2 and C677T polymorphisms were determined in all participants. The study protocol was reviewed and approved by the Human Ethical Committee, and Medical Research Council of the Instituto Mexicano Del Seguro Social, and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed written consent was obtained from all subjects before enrolment.

Results: There was a significant difference in the PIA1/A2 genotype distribution (P =0.001) and allele frequency (P=0.001), between myocardial infarction and control groups, but not in the PIA1/A2 genotype distribution (P = 0.67) and allele frequency (P=0.85), between stroke. In contrast, there was a significant difference in the C677T genotype distribution (P=0.001) and allele frequency (P=0.001), between stroke and control group, but not in the C677T genotype distribution (P=0.60) and allele frequency (P=0.42), between myocardial infarction and control group.

Conclusion: The allele PIA2 represented an independent risk for myocardial infarction but not for stroke. In contrast, the C677T polymorphism was associated with increased risk for stroke but for myocardial infarction. Our results suggest a possible different role of genetics factors on atherothrombotic disease such as myocardial infarction and stroke. In one territory may be associated, whereas in other may be protector. More comparative studies are needed to highlight similarities and differences between the pathophysiology of myocardial infarction and stroke and how those differences may affect decision regarding to therapy and secondary prevention strategies.

Disclosure of Interest: None Declared

P17
THE ANGIOTENSIN-CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM IS ASSOCIATED WITH INCREASED RISK FOR IDIOPATHIC ISCHEMIC STROKE BUT NOT FOR MYOCARDIAL INFARCTION IN YOUNG MEXICAN POPULATION

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Problem Statement: Myocardial infarction and stroke represent the most important thrombosis complications of arterial thrombosis disease. Between 5 and 10 % of individuals who suffer MI or stroke are 45 years of age or less and it represents a very important health care issue worldwide. Several conditions may contribute to the occurrence of those atherothrombotic diseases in this age group, including environmental and genetic risk factors. In these two independent case-control studies, we examined the association of insertion/deletion polymorphism on the angiotensin-converting enzyme gene with myocardial infarction or stroke in a young Mexican population.

Method: In a first case–control study 297 consecutive patients less than 45 years old who had survived their first myocardial
infarction were included. The diagnosis of myocardial infarction was based on an electrocardiogram, clinical data and laboratory. They were admitted to the Intensive Coronary Care Unit of the Cardiology Hospital, Centro Médico Nacional Siglo XXI, in Mexico City, Mexico. A total of 297 Mexican subjects without personal history of myocardial infarction, age-gender matched, were included in the control group. In a second independent case-control study, a total of 235 consecutive unrelated patients less than 45 years of age, with diagnosis of stroke were enrolled in the present study. Diagnosis of idiopathic ischemic stroke was considered in all patients after an acute focal neurological deficit with duration greater than 24 h and followed by confirmation by means of brain-computed tomography or magnetic resonance. A total of 235 Mexican subjects without personal history of stroke, age-gender matched, were included in the control group. The insertion/deletion polymorphism was determined in all participants. The study protocol was reviewed and approved by the Human Ethical Committee, and Medical Research Council of the Instituto Mexicano Del Seguro Social, and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed written consent was obtained from all subjects before enrolment.

Results: There was significant difference in the insertion/deletion genotype distribution (P =0.02) and allele frequency (OR=1.45, 95%CI 1.0-2.74, P=0.02), between idiopathic ischemic stroke and control groups, in contrast, there was a similar insertion/deletion genotype distribution (P=0.65) and allele frequency (P=0.67), between myocardial infarction and control groups. Hypertension, smoking, and family history of atherothrombotic disease were also associated with increased risk for myocardial infarction and idiopathic ischemic stroke. Conclusion: The angiotensin-converting enzyme insertion/deletion polymorphism represented an independent risk factor for idiopathic ischemic stroke but not for myocardial infarction in young Mexican individuals. Our results suggest a possible different role of genetics factors on atherothrombotic disease such as myocardial infarction and stroke. In one territory may be associated with an increased risk, whereas in other may represent a protector factor. The identification of 'at risk' individuals by genetic mapping of susceptible genes for effective control of other host factors will be a very effective and practical approach for prevention, as well as the development of improved therapy for patients.

Disclosure of Interest: None Declared

P18
SUPERIORITY OF PROPHYLAXIS VERSUS ON-DEMAND THERAPY WITH PLASMA-PROTEIN-FREE RECOMBINANT FACTOR VIII FORMULATED WITH SUCROSE (BAY 81-8973): LEOPOLD II STUDY RESULTS

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Problem Statement: Factor VIII (FVIII) products are administered to patients with hemophilia A to prevent bleeds (prophylaxis) or on demand when bleeding events occur. Compared with on-demand treatment, prophylaxis regimens decrease bleeding frequency, preserve joint function, and improve health-related quality of life. The aim of the current study was to demonstrate the superiority of prophylaxis versus on-demand therapy with BAY 81-8973, a new full-length recombinant FVIII product, in patients with severe hemophilia A. Method: This phase 2/3, randomized, open-label, crossover study was a part of the LEOPOLD program and included males aged 12–65 years with severe hemophilia A with ≥150 exposure days to any FVIII product and no history of FVIII inhibitors. Patients were randomized into a prophylaxis low-dose arm (20–30 IU/kg 2x weekly), a prophylaxis high-dose arm (30–40 IU/kg 3x weekly), or an on-demand arm; BAY 81-8973 potency assignments were based on the chromogenic substrate assay or adjusted to the one-stage assay. The primary efficacy endpoint was the annualized number of all bleeds; annualized spontaneous bleeds were also assessed. Safety endpoints included adverse events (AEs) and immunogenicity.

Results: Of the 80 treated patients (mean age, 29.6 years), 21 received on-demand treatment, 28 received low-dose prophylaxis, and 31 received high-dose prophylaxis. The median (range) nominal dose was 32 (21–42) IU/kg/injection for prophylaxis injections in the combined prophylaxis groups and 22 (11–35) IU/kg/injection for treatment of bleeds in the on-demand group. The median (quartile 1 [Q1]; quartile 3 [Q3]) annualized number of all bleeds in the on-demand group (60.0 [41.7; 76.3]) was markedly higher than that in the prophylaxis groups (low dose, 4.0 [0; 8.0]; high dose, 2.0 [0; 4.9]; combined, 2.0 [0; 7.0]). The comparisons between the on-demand group and the different prophylaxis groups (low dose, high dose, and combined) showed significant differences (P<0.0001 for all comparisons), demonstrating the superiority of prophylaxis versus on-demand therapy with BAY 81-8973. Median (Q1; Q3) annualized number of spontaneous bleeds in the on-demand group (42.1 [24.3; 61.3]) was higher than in the prophylaxis groups (low dose, 2.0 [0; 6.5]; high dose, 0 [0; 3.0]; combined, 1.0 [0; 4.0]). Incidence of treatment-related AEs was low (4%), and no treatment-related serious AEs or inhibitors were reported. Conclusion: Patients with severe hemophilia A receiving high-dose (3x weekly) or low-dose (2x weekly) BAY 81-8973 prophylaxis had a significantly lower annualized number of bleeds compared with on-demand therapy, confirming the superiority of prophylactic treatment over both regimens. BAY 81-8973 also exhibited good tolerability.

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P19
SIMPLIFIED CRB-65 FOR RISK STRATIFICATION AND PREDICTING PROGNOSIS IN ACUTE PULMONARY EMBOLISM

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Problem Statement: Pulmonary embolism (PE) and community acquired pneumonia (CAP) are potentially life-threatening diseases. In CAP CRB-65 is used for risk stratification and prognosis prediction. The aim of this study...
was to examine a simplified CRB-65 (sCRB-65) for predicting prognosis in PE.
Method: We retrospectively analyzed the data of 182 PE patients. Patients were, according to the score of sCRB-65 (respectively 1 point for dyspnoea, systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg, age ≥65years), subdivided in risk-classes 1-4. Risk classes were compared with Kruskal-Wallis test. Logistic multivariable regression and Pearson correlation matrix were calculated for coherence of sCRB-65 and in-hospital death, right ventricular load and PE severity stadium.
Results: PE severity stadium, systolic pulmonary artery pressure (sPAP) and frequency of in-hospital death increased with growing risk class. Risk class 1 showed lower PE severity stadium than 2 (P=0.0253), 3 (P=0.0132) and 4 (P=0.00162), lower percentage of patients with sPAP>30mmHg than 2 (0%vs.48.9%, P=0.0419), 3 (0%vs.70.8%, P=0.00112) and 4 (0%vs.75.0%, P=0.0113). Frequency of in-hospital deaths was higher in risk class 4 than in 1 (P=0.0024), 2 (P=0.00014) and 3 (P=0.000058). Multivariable logistic regression showed an association between sCRB-65 scored>0 and PE severity stadium (OR11.42,95%CI:1.35 -96.66,P=0.0254), RVD (0%vs.48.9%,P=0.0419), 3 (0%vs.70.8%, P=0.00112) and 4 (0%vs.75.0%,P=0.0113). Frequency of in-hospital deaths was higher in risk class 4 than in 1 (P=0.0024), 2 (P=0.00014) and 3 (P=0.000058). Multivariable logistic regression showed an association between sCRB-65 scored>0 and PE severity stadium (OR11.42,95%CI:1.35 -96.66,P=0.0254), RVD (OR10.09,1.16-87.78,P=0.0363) and sPAP (OR1.08,1.02-1.15,P=0.0092) as well as a trend towards significance (OR12.39,0.90-171.34,P=0.060) between in-hospital death and sCRB-65. sCRB-65 correlated with PE severity stadium (OR12.39,0.90-171.34,P=0.060) and the right heart as well as prognosis. Normotensive PE patients <65years without dyspnoea have the best prognosis.

Disclosure of Interest: None Declared

P21
COMPARISON OF PHARMACODYNAMICS BETWEEN LOW DOSE TICAGRELOR AND CLOPIDOGREL AFTER LOADING AND MAINTENANCE DOSES IN HEALTHY KOREAN SUBJECTS
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Problem Statement: Relatively high dose of ticagrelor is recommended to exert a faster and more powerful inhibition of platelet aggregation in comparison to clopidogrel, however, whether this is suitable for Asian ethnicity remains to be investigated. The aim of this study was to assess the effects of low loading doses (LD, 90 mg) and maintenance doses (MD, 90mg daily) of ticagrelor in comparison to clopidogrel (600 mg LD, 75 mg daily MD) in healthy Korean volunteers.
Method: Twelve subjects were randomized into two groups, receiving either clopidogrel or ticagrelor. Platelet aggregation assessment was conducted using 3 methods including traditional light transmission aggregometry (LTA), the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) and the multiple electrode platelet aggregometry (MEA, Dynabyte Medical, Munich, Germany).
Results: The assay results produced by the other two platelet function tests (VerifyNow and MEA) were similar to those obtained by LTA. The mean IPA to 10 µM ADP in the ticagrelor group was significantly higher than clopidogrel group at the 0.5, 2, 6, 26, and 122 hour time points (p<0.001) while no significant difference was detected between the two groups at the 24 and 120 hour time points (p>0.05). The assay results produced by the other two platelet function tests (VerifyNow and MEA) were similar to those obtained by LTA.

Conclusion: The ticagrelor (90 mg LD, 90 mg daily MD) cause a more rapid and potent inhibition of platelet function when compared to clopidogrel (600 mg LD and 75 mg MD). Also, the lowest value of platelet inhibition at the 24 hour after ticagrelor 90 mg single ingestion was as effective as clopidogrel 75 mg at maintenance dose.

Disclosure of Interest: None Declared

P20
CARDIAC TROPONIN I FOR PREDICTING RIGHT VENTRICULAR DYSFUNCTION AND INTERMEDIATE RISK IN PATIENTS WITH NORMOTENSIVE PULMONARY EMBOLISMS
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Problem Statement: Right ventricular dysfunction (RVD) and troponin are important for accurate risk stratification in acute pulmonary embolism (PE). The aim of this study was to investigate the association of RVD and Troponin I in normotensive patients with acute PE and to calculate a predictive cut-off value for Troponin I level predicting RVD and for predicting intermediate risk (sub massive PE).
Method: Retrospective analysis of clinical, laboratory, radiological and echocardiographic data of normotensive patients with PE (2006-2011) was performed. According to echocardiography patients were categorized in PE group with RVD or without RVD. Groups were compared focused on Troponin I. Effectiveness of Troponin I for predicting RVD and for intermediate risk (sub massive PE) was tested. Receiver Operating Characteristic (ROC) curves and cut-off values were calculated.
Results: 129 normotensive PE patients (77 women) 71 with and 58 without RVD were included in this study. Patients with RVD were older (75.0years (61.3/81.0) vs. 66.0years (57.7/75.1), P=0.019), Troponin I (0.06ng/ml (0.02/0.23) vs. 0.01mg/ml (0.00/0.03), P<0.0001) and D-Dimer (2.00mg/l (1.08/4.05) vs. 1.23mg/l (0.76/2.26), P=0.016) were elevated in PE with RVD. Troponin I was associated with RVD (OR, 3.95; 95%CI: 1.95-8.02, p=0.00014). Area under the curve of the ROC curve for diagnosing RVD was 0.79 for Troponin I predicting RVD and 0.87 for predicting intermediate risk (sub massive PE). Cut-off values for Troponin I predicting RVD and sub massive PE was respectively 0.01ng/ml with negative predictive value of respectively 73%. Conclusion: In normotensive PE patients, Troponin I is helpful for risk stratification and especially for ruling out RVD.

Disclosure of Interest: None Declared
The relationship between highly-sensitive troponin-I and mean platelet volume in patients with acute myocardial infarction

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Problem Statement: The measurement of cardiac specific troponins is pivotal in the diagnostic and prognostic approach of patients with acute myocardial infarction (AMI). The mean platelet volume (MPV) and platelet counts (PLT) are indicators of thrombotic potentials and independent risk factors for recurrent vascular events. Highly-sensitive (HS) serum cardiac troponin-I (hs-TnI) is a new biochemical marker of myocardial damage with high specificity and sensitivity. The aim of this study was to find out the level of hs-TnI and identify its correlation with MPV and PLT in patients with acute myocardial infarction.

Method: This study involving 28 patients with AMI (17 male, 11 female). AMI was diagnosed if at least two of the following criteria were present: cardiac chest pain, ST segment elevation of at least 2 mm in chest leads or 1 mm in limb leads, and raised creatine kinase MB activity. No control subjects were taken because hs-TnI not detected in the peripheral circulation under normal circumstances. Troponin-I levels were measured by a commercial chemiluminescent microparticle immunoassay (CMIA) (Architect stat Troponin-I P, Abbott Laboratories, Abbott Park, IL, USA), for which the cut-off value for detection of myocardial infarction or ischemic damage is set by the manufacturer at 0.3 ng/mL. MPV and PLT was measured on the Cell-Dyn Ruby analyzer (Abbott Diagnostics).

Results: Mean age of study group was 64.4±15.3 years with 60.7% being male. Serum hs-TnI was elevated in 92.9% of cases. The mean serum concentration of hs-TnI was 76.91±28.4 ng/mL (min.0.37 ng/mL; max.614.46 ng/mL). The mean platelet count (PLT) was elevated in 3.6% of cases. The mean PLT for the patients with AMI was 245.32±14.28 x 10⁹/L. The mean platelet volume (MPV) was elevated in 7.14% of cases. The mean platelet volume (MPV) was 8.35±0.26 fL. There was no statistically significant relationship between hs-TnI level and MPV (r= 0.219; p=0.287).

Conclusion: This study revealed elevated hs-TnI and reference values of PLT and MPV in most patients with acute myocardial infarction. There was no statistically significant relationship between elevated hs-TnI and PLT, and between elevated hs-TnI and MPV. Based on these findings, hs-TnI shows excellent promise as a specific marker for AMI detection. However, plateau indices (PLT and MPV) cannot be used as markers for AMI. The potential role of platelet indices in AMI remains to be investigated by a multi-institutional level to verify the possible clinical significance of this finding.

Disclosure of interest: None Declared

Frequency and nature of non-compliant samples for coagulation testing

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Problem Statement: Like in other areas of laboratory diagnostics, preanalytical phase represents the major source of errors in coagulation testing, too. The most errors in the preanalytical phase of coagulation testing are caused by inappropriate and unacceptable samples. The aim of this study was to evaluate the frequency and nature of sample non-conformities for coagulation testing during a period of 1 year (from January 2013 to December 2013).

Method: As our laboratory is accredited in accordance with ISO 15189 standard for years, we routinely and continuously record all non-compliant samples for coagulation testing. All sample non-conformities are classified into the following categories: clotted sample, inappropriate ratio of anticoagulant to blood (under filled sample), hemolyzed sample, insufficient sample quantity for all requested tests, missing sample, lipemic sample, improperly labelled sample (mislabeled or unlabeled) and sample contaminated with heparin. We evaluated the frequency of individual categories of non-compliant samples mentioned above during the overall study period of one year.

Results: A total of 62275 patient protocols for coagulation testing were received at our laboratory during a period of 1 year and a total of 848 samples or 1.4% (848/62275) were recorded as non-compliant. Among all non-compliant samples, clotted specimen was the most common cause for the rejection (381/848; 44.9%), followed by an inappropriate blood to anticoagulant ratio (205/848; 24.2%). The frequencies of other sample non-conformities were as follows: severe haemolysed samples (hemoglobin>2 g/L) inappropriate for corrective action by measuring global tests (PT; APTT; TT; fibrinogen) at alternative higher wavelength (570nm) or even slightly hemolyzed samples for all other tests (115/848; 13.6%), missing samples (68/848; 8%), insufficient sample quantity (30/848; 3.5%), samples contaminated with heparin (29/848; 3.4%), lipemic samples inappropriate for measuring global tests at alternative wavelength (11[848; 1.3%] and mislabeled or unlabeled samples (9/848; 1.1%). No significant differences in the ratio of individual categories of sample non-conformities were found between the observational 12 months (P=0.443) and clotted sample was found to be a leading cause of sample non-conformity in all 12 months (P<0.001).

Conclusion: The present study confirmed the relative frequency of sample non-conformities for coagulation testing to be 1.4%, a rate that is congruous to that previously reported in the literature. Clotted sample was the most common cause of sample non-conformities for coagulation analysis. Although hemolysis is usually recorded as the leading cause of unsuitable samples for coagulation testing, it was not the case in our study. We assume that it is because we routinely use as a corrective action alternative measurement of global coagulation tests at higher wavelength for slightly and moderately (hemoglobin up to 2 g/L) hemolytic samples which significantly reduced the rate of hemolytic samples as non-compliant. Since coagulation assays are extremely
sensitive to different pre-analytical variables that mostly include sample collection procedures, good knowledge and continuous documentation of these variables, as well as proper education of all persons involved in this process, including laboratory personnel and those outside the laboratory, is crucial for reducing errors and obtaining reliable results of coagulation tests.

Conclusion: A significant number of VTE patients with increased FVIII activity, i.e. for hemiplegia=2, malignancy=2, epilepsy=1. Further, for a minority of VTE patients with increased FVIII levels: pregnant women=7, CAD=3, CVI=2, miscarriage=8, infertility=6, epilepsy=2, hemiplegia=2, malignancy=2. A total of 38 patients had increased FVIII and 91 patients had FVIII levels within reference range (70-150%). Of the 38 subjects with increased FVIII, 21 had a single episode of VTE; deep venous thrombosis (DVT) =12, pulmonary embolism (PE) =9. Frequency of increased FVIII among all VTE patients was 26.6% (21/79), mean±SD age 46±13.9 years, 11 males and 10 females, mean±SD FVIII level 193.2±17.6%. FVIII values were not statistically different between patients with DVT (189.1±19.7%) and PE (199.0±13.4%), P=0.224. For all VTE patients testing for FVIII was requested for 10 pregnant women, of which even 7 had increased FVIII activity. Since it is well known that FVIII levels are physiologically increased during pregnancy and puerperium, testing for FVIII as thrombophilic risk factor should be delayed for at least 6 weeks postpartum. Further, except for VTE patients, FVIII was requested as part of thrombophilia testing also in clinical conditions other than VTE. Finally, but not least, for a minority of VTE patients with an initial positive result for FVIII (>150%), testing was repeated after 3 to 6 months, in order to confirm a persistent constitutional increased FVIII over time and not due to an acute phase response. Based on the results in our patient population it is obvious that laboratory has to take more substantial role in the investigation process of FVIII as thrombophilic risk factor, pointing the importance of determining FVIII in accordance with the recommended guidelines related to the questions who and when to test, all in order to obtain accurate and reliable test result.

Disclosure of Interest: S. Margetic Employee of: None declared, B. Getaldic: None Declared, D. Ruzic: None Declared, I. Vuga: None Declared, N. Vrlic: None Declared

P24 ANALYSIS OF FACTOR VIII ACTIVITY IN PATIENTS REFERRED FOR THROMBOPHILIA TESTING
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Problem Statement: Since persistently increased plasma level of factor VIII (FVIII) above 150% has been recognized as an independent risk factor for venous thromboembolism (VTE), measurement of this coagulation factor should also be included in routine thrombophilia testing. The aim of this study was to evaluate the results of FVIII activity in unsel ected consecutive patients referred for thrombophilia testing during a one year period (from January 2013 to December 2013).

Method: FVIII activity was measured using one-stage APTT-based coagulometric method (Actin FS, FVIII deficient plasma, Siemens, Germany) on BC3XP analyzer (Siemens, Germany).

Results: FVIII assay was requested for a total of 129 patients as a part of thrombophilia testing with following clinical conditions: VTE=79, cardiovascular disease (CAD) =12, pregnancy=10, cerebrovascular insult (CVI) =8, miscarriage=8, infertility=6, epilepsy=2, hemiplegia=2, malignancy=2. A total of 38 patients had increased FVIII and 91 patients had FVIII level within reference range (70-150%). Of the 38 subjects with increased FVIII, 21 had a single episode of VTE; deep venous thrombosis (DVT) =12, pulmonary embolism (PE) =9. Frequency of increased FVIII among all VTE patients was 26.6% (21/79), mean±SD age 46±13.9 years, 11 males and 10 females, mean±SD FVIII level 193.2±17.6%. FVIII values were not statistically different between patients with DVT (189.1±19.7%) and PE (199.0±13.4%), P=0.224. For all VTE patients testing for FVIII was requested for 10 pregnant women, of which even 7 had increased FVIII activity. Since it is well known that FVIII levels are physiologically increased during pregnancy and puerperium, testing for FVIII as thrombophilic risk factor should be delayed for at least 6 weeks postpartum. Further, except for VTE patients, FVIII was requested as part of thrombophilia testing also in clinical conditions other than VTE. Finally, but not least, for a minority of VTE patients with an initial positive result for FVIII (>150%), testing was repeated after 3 to 6 months, in order to confirm a persistent constitutional increased FVIII over time and not due to an acute phase response. Based on the results in our patient population it is obvious that laboratory has to take more substantial role in the investigation process of FVIII as thrombophilic risk factor, pointing the importance of determining FVIII in accordance with the recommended guidelines related to the questions who and when to test, all in order to obtain accurate and reliable test result.

Disclosure of Interest: None Declared

P25 ANTIPLATELET DRUG RESISTANCE IN ASIAN POPULATION
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Problem Statement: Clopidogrel, in combination with Aspirin, is currently the standard of care for patients undergoing PCI. Many clinical trials have shown that, in high-risk patients, prolonged dual antiplatelet treatment is more effective than Aspirin alone in preventing MACE. However, despite the use of such therapy, a considerable number of patients continue to have recurrent thrombotic events. Previous studies have shown a significant inter-individual variability in platelet response to Clopidogrel therapy in patients with CAD. Clopidogrel is the commonly used P2 Y12 receptor antagonist used in the treatment of ischemic heart disease and stroke. Poor metabolizers treated with Clopidogrel exhibit higher cardiovascular event rates. Asian population has been found to show higher resistance to Clopidogrel.

Method: Present study was undertaken to find the prevalence of Aspirin and Clopidogrel resistance in patients undergoing coronary angioplasty. 200 consecutive patients who underwent coronary angioplasty for acute coronary syndrome were selected for the study. All patients had 300 mg Aspirin and 600 mg for Clopidogrel as loading dose. 150 mg Aspirin and 75 mg twice daily of Clopidogrel were given as the maintenance dose. VerifyNow point of care platelet function study were done 5 days after the loading dose of Clopidogrel. Aspirin resistance was defined as more than 213 platelets per minute and Clopidogrel resistance is defined more than 213 platelets resistance units. Results: 84.8 % were male subjects 15.2% were women. 50.3 % were diabetics. 27.2% patients were Aspirin resistant and 33.8% were resistant to Clopidogrel. 7% showed dual antiplatelet resistance. Clopidogrel resistance was more common in female (P value <0.001). Clopidogrel resistance was significantly more common than Aspirin resistance in diabetic subjects.

Conclusion: Aspirin and Clopidogrel resistance are common in Asian population. This should be taken into account in selecting antiplatelet drugs in patients following acute myocardial infarction irrespective of the management strategy. It is surprising that correlation between Aspirin/Clopidogrel resistance, genetic polymorphism, and clinical data do not correlate to explain the long term benefits of drug therapy.

Disclosure of Interest: None Declared
CiTH

P26
D-DIMER KINETICS, CHEMOTHERAPY AND THE RISK OF BLEEDING IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Hematology Oncology, Medical College of Wisconsin, Milwaukee, United States

Problem Statement: Newly diagnosed Acute Promyelocytic Leukemia (APL) is a medical emergency because of the high risk of haemorrhage. Initiation of All-Trans Retinoic Acid (ATRA) is required to normalize APL-mediated coagulopathy. However, there is an initial period when the risk of coagulopathy and bleeding may increase. In addition to ATRA, remission induction in therapy for APL also includes cytotoxic chemotherapy (CC) i.e. anthracycline or Arsenic Trioxide (ATO). We hypothesize that patients who receive CC as a part of their induction regimen have worsened coagulopathy and clinically significant bleeding when compared to those who received ATO instead.

Method: With institutional review board (IRB) approval, the charts of patients with APL who were treated with induction therapy at our institution from July 2007 to December 2013 were reviewed. We collected demographic data, coagulation parameters, and any bleeding events that occurred at presentation or during therapy.

Results: 27 patients were identified with median age 50 and 11 male. 11 were treated without CC. Nine patients had bleeding complication during therapy (Table 1) and seven of these received CC. Of the seven patients, only one had bleeding at the time of diagnosis. These 7 patients had risk scores of high (2), intermediate (2), and low (3). The 2 patients that did not receive CC had bleeding as their initial presentation (1-high, and 1-intermediate risk). We then evaluated the D-Dimer kinetics of patients treated with and without CC. Most patients initially presented with high D-Dimer levels but it improved during the 3-4 days following initiation of therapy in patients who were treated with ATO and ATRA (Figure 1). However, patients treated with ATRA and CC had a second rise in their D-Dimer levels after the start of therapy (Figure 2). This second spike correlated with clinically significant bleeding in 85% of the patients.

Disclosure of Interest: None Declared

P27
VENOUS THROMBOEMBOLISM PROPHYLAXIS IN INTENSIVE CARE UNIT PATIENTS: FINDINGS OF THE BRAZILIAN REGISTRY
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1Saude da Familia, Faculdade de Medicina da Bahia da Universidade Federal da Bahia, Salvador, 2Medicina, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Problem Statement: Approximately one-fourth of hospitalized patients passes through an intensive care unit (ICU) while acutely ill. Venous thromboembolism (VTE) in the ICU is associated to poorer outcomes; hence, starting appropriate VTE prophylaxis is essential. The profilaxiatetv.org is an online registry linked to the University Hospital of the FMUSP that offers VTE risk-assessment for patients in Brazilian hospitals initiating VTE prophylaxis programs. We evaluated the VTE risk and use of prophylaxis in this registry focusing on ICU patients.

Method: We evaluated data from cross-sectional audits in 113 participating hospitals from 6/2008 till 2/2014. Data on VTE risk factors (RF), contra-indications (CI) for pharmacologic prophylaxis, and use of prophylaxis were entered by local hospitals. The risk-assessment for surgical patients was based on the 2008 American College of Chest Physicians (ACCP) guidelines and for medical patients was based on the Brazilian Guideline for VTE prophylaxis (2006).

Results: A total of 66,221 patients were registered; 18,4% (12,216) were ICU patients; 50% were female, 73% had age 40, and 60% age ≥ 55 years-old; 75% (9,111) were medical

Table 1:

<table>
<thead>
<tr>
<th>Patients with bleeding on chemotherapy</th>
<th>Peak D-Dimer level on the day of bleed</th>
<th>Platelets &lt; 50</th>
<th>Clot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>Yes - 9</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>no</td>
<td>Yes - 48</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

This is the first report of bimodal D-Dimer kinetics and associated bleeding diathesis in patients with APL whose induction therapy includes CC in contrast to those treated without traditional cytotoxic agents. Although the sample size is small, this clinically significant increase in bleeding risk among patients treated with ATRA + CC supports strong consideration of using alternative agents to treat patients with to treat patients with APL, and highlights the importance of close haemostatic monitoring during the early stages of a patient’s treatment for APL. If confirmed in larger studies, pro-haemostatic treatments like anti-fibrinolytic therapy could be considered in patients with second elevation in D-Dimer.

Disclosure of Interest: None Declared

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References:
3. Prophylaxis, and use of prophylaxis were entered by local hospitals. The risk-assessment for surgical patients was based on the 2008 American College of Chest Physicians (ACCP) guidelines and for medical patients was based on the Brazilian Guideline for VTE prophylaxis (2006).
4. Profilaxiatetv.org is an online registry linked to the University Hospital of the FMUSP that offers VTE risk-assessment for patients in Brazilian hospitals initiating VTE prophylaxis programs. We evaluated the VTE risk and use of prophylaxis in this registry focusing on ICU patients.

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Image:
cases, 90% of which had high risk for VTE; 25% (3,105) were surgical cases: 81% were high risk and 11% moderate risk patients. The vast majority (97% surgical and 99% medical) had at least one RF for VTE. The most common (Table 1) were age >55, infection, venous catheters, respiratory insufficiency, stroke, MI, heart failure, obesity and previous VTE. Relative CI for prophylaxis were present in 18% (active bleeding 8%, coagulopathy 3%, severe renal insufficiency 2%, use of other anticoagulant 2%, other 2%). VTE prophylaxis was used in 71%: pharmacological in 59% (unfractionated heparin 6%, low-molecular weight heparins 83%, other in 11%) and mechanical in 12%; combined methods in 20%. Mechanical methods included intermittent compression devices 10%, elastic stockings 13% and physiotherapy to the legs in 87%. Complications of prophylaxis were registered in only 0.2% of the cases. Conclusion: The vast majority of ICU patients in Brazil have high risk for VTE and 71% received prophylaxis. Routine evaluation of risk upon ICU admission using an opt-out rule for prophylaxis may improve implementation of guidelines and avoid complications, once 18% present some CI for pharmacological prophylaxis. The evaluation of VTE and bleeding risks is paramount for the adequacy of prophylaxis in ICU patients, and should be performed daily. Providing instructions for continuing prophylaxis upon ICU discharge may be an opportunity for improvement when patients are transferred to other wards.

**Table 1. Padua risk assessment model (high risk of VTE: ≥4)**

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer*</td>
<td>3</td>
</tr>
<tr>
<td>Previous VTE (with the exclusion of superficial vein thrombosis)</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility**</td>
<td>3</td>
</tr>
<tr>
<td>Elderly age ≥70 years</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
</tbody>
</table>

**Conclusion:** More than half of hospitalized medical patients are at-risk for VTE. The BG offers an easy-to-use algorithm for risk assessment without the need for score calculation. Although there is some variability, the BG performs similarly to the PS, agreeing in 90.2% of the cases. The evaluation of VTE risk is paramount for the adequacy of prophylaxis. The BG algorithm offers a valid alternative for risk assessment in medical patients.

Problem Statement: Platelets transfusions have the main goal to stop and/or to prevent a bleeding. However, platelet concentrate storage leads to changes in platelet hemostatic activity. We studied clot properties formed from some platelets concentrates (PCs) in varied storage time.

Method: After apheresis and leukoreduction procedures, platelets were suspended in autologous plasma (n=26), or in platelet additive solution, PAS (up to 60-70 vol%; SSP+; n=24). 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: Glucose consumption, pH, lactate production had main differences for PCs suspended in diverse medias. In stored PCs suspended in autologous plasma the formed clot demonstrated both gradual reduced elasticity and deformability starting from second day. From the third storage day platelets lost their meaning for clot properties. PCs suspended in PAS have shown the depression for platelets aggregability and adhesion. Activated platelets had no impact to clot properties during full storage time. Total decline of clot quality including low elasticity and impaired deformability were found starting from 3rd storage day compared to the day of proceeding.

Conclusion: Clot properties (elasticity and deformability) are forming in PCs at the day of proceeding. Clot changes observed in PCs does not depend directly from platelets aggregability and adhesion. Therefore we assume that successful recovery of in vivo platelet functional activity determines total hemostatic effect of platelet transfusion. Now this assumption is verified in the following study.

Disclosure of Interest: None Declared

A NOVEL USE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN THE MANAGEMENT OF PROSTHETIC VALVE THROMBOSIS DURING PREGNANCY

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Problem Statement: To highlight the potential complications of switching from warfarin to a heparin-based anticoagulant in the management of mechanical heart valve during pregnancy, and how extracorporeal membrane oxygenation (ECMO) may play a role in resuscitation for surgery.

Method: A 27-year-old pregnant woman (at 28 weeks gestation) with a 6-year old mechanical mitral valve presented to local emergency department complaining of severe shortness of breath. At the start of pregnancy the patient had discontinued warfarin in-favor of low molecular weight heparin anticoagulation as replacement therapy, self-administering subcutaneous therapeutic enoxaparin injections twice daily. Her condition quickly deteriorated after admission and she was referred for ECMO, intensive care support, assessment for possible caesarean section and delivery of the fetus.

Results: Transoesophageal echocardiogram confirmed prosthetic valve thrombosis and the patient was converted from veno-venous (VV) ECMO to veno-arterial (VA) ECMO, stabilized for 5-hours and taken to theatre for emergency mitral valve placement, this time with a tissue valve. Fetal heart sounds were undetectable upon initial arrival and the decision was made to medically induce the deceased fetus several days after the operation. The patient post-operatively remained on ECMO for 7 days and was subsequently discharged to the ward.

Conclusion: Anticoagulation during pregnancy is a complex issue and often has lapses in compliance. In this case prosthetic valve thrombosis was managed effectively with a combination of VV-VA ECMO. We aim to discuss in detail the problem of prosthetic valve thrombosis, anticoagulation in pregnancy and problems of using ECMO in this setting. ECMO provides effective alternative approach to stabilize high-risk patients before emergent cardiac surgery.

Disclosure of Interest: None Declared

SAFETY AND EFFICACY OF BAY 81-8973 FOR PROPHYLAXIS AND TREATMENT OF BLEEDS IN PREVIOUSLY TREATED CHILDREN WITH SEVERE HEMOPHILIA A: RESULTS OF THE LEOPOLD KIDS STUDY, PART A

Rolf Ljung1,2, Gili Kener3, Elena Santagostino4, Valeria Kaleva4, Luminita Rusen5, Despina Tsenekadou-Stoeter6, Lisa A. Michaels4, Anita Shah7, Walter Hong8 and on behalf of the investigators of the LEOPOLD Kids trial

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Problem Statement: BAY 81-8973 is a new full-length recombinant factor VIII (FVIII) product in development for treatment of hemophilia A. The aim of this study was to demonstrate the safety and efficacy of BAY 81-8973 for prophylaxis and treatment of bleeds in previously treated children with severe hemophilia A.

Method: This phase 3, multicenter, open-label, randomized study was part of the LEOPOLD clinical trial program. Part A of this 2-part study included boys aged ≤12 years with severe hemophilia A with ≥50 exposure days (EDs) to any FVIII product and no history of FVIII inhibitors. Patients received BAY 81-8973 prophylaxis 25–50 IU/kg ±2 times weekly. The study continued until ≥50 EDs were achieved per patient (approximately 6–8 months), with an optional extension phase to allow observations for ≥100 EDs. Enrolment of patients was staggered, beginning with patients aged 6–12 years followed by patients aged <6 years. The primary efficacy endpoint was the annualized number of total bleeds that occurred within 48 hours of the previous prophylaxis injection. Additional efficacy variables included the annualized number of total bleeds, joint bleeds, and spontaneous bleeds. Safety endpoints included adverse events (AEs) and immunogenicity.

Disclosure of Interest: None Declared
Method: The LEOPOLD trials enrolled patients aged 12–65 years (LEOPOLD I and II) or ≤12 years (LEOPOLD Kids) with severe hemophilia A, ≥150 (LEOPOLD I and II) or ≥50 (LEOPOLD Kids) concentration (Cmax) and area under the curve (AUC) values for adolescents were within the range of values seen for adults; PK values were slightly lower for children compared with adults. PK analyses in the different ethnic subgroups in the 3 trials showed that the AUC and Cmax values for Chinese and Japanese patients were within the range of values seen for non-Asian patients.

Conclusion: The PK profile of BAY 81-8973 was non-inferior to rFVIII-FS. The PK results were similar following single and repeated dosing and across ethnic groups in the 3 LEOPOLD trials.

Disclosure of Interest: A. Shah Employee of: Bayer HealthCare, H. Delesen Employee of: Bayer Pharma AG, S. Lalezari Consultant for: Previously received honoraria from Bayer

P32 ANALYSIS OF CAROTIDENDOBIC STROKE SEVERITY AT ONSET AND PRIOR ANTITHROMBOTIC THERAPY
Sargylana A. Chugunova1, Andrian N. Slepctov2, Tatiana Y.Nikolaeva1

Problem Statement: Antithrombotic therapy is used for the prevention of ischemic cardiac embolic stroke (CS) due to atrial fibrillation (AF). Anticoagulation with a vitamin K antagonist and, in special cases, aspirin is recommended for prevention of CS in patients with AF (Furie K.L. et al., 2010). Among patients who were taking warfarin, an INR < 2.0 at admission, as compared with an INR of 2.0 or greater, increased a severe stroke and the risk of death within 30 days (Hyylek E.M. et al., 2003). The aim of this study was to evaluate the onset severity of cardio embolic stroke, depending on the prior anticoagulation or antiplatelet therapy.

Method: 103 acute CS patients with AF admitted to the Regional Vascular Centre (Yakutsk) in 2013 were included in the observed group. All patients were screened including the examination of an experienced neurologist, neuroimaging (CT and / or MRI), electrocardiography, heart ultrasound, examination of cardiologist, blood coagulation tests. The presence of preceding antithrombotic therapy was identified from the information of the patient and / or relatives. Stroke severity was scored using NIHSS (National Institutes of Health Stroke Scale) at the onset of the disease before the starting of antithrombotic therapy in the hospital. Statistical analysis. Quantitative signs were described by medians (Me) and quartiles [Q1; Q3]. For comparison of the parameters of the two groups non-parametric method U-Mann-Whitney test was used.

Results: In the study group (n=103) there were 49 males (47.6%). There were 53 Caucasians (51.5%) and 50 Asians (48.5%). Mean age was 71 [64; 77] years. All patients had AF, including 100 patients with non-valvular AF (97.1%) and 3 patients with secondary AF due to the chronic rheumatic heart disease (2.9%). Permanent AF was diagnosed in 78 untreated patients is ongoing. The main study results from part A are presented here.

Results: Of 51 treated patients, 25 were aged <6 years and 26 were aged 6–12 years. A total of 134 injections of BAY 81-8973 were administered for treatment of 97 bleeds. The median (quartile 1 [Q1]; quartile 3 [Q3]) annualized number of total bleeds within 48 hours of the previous prophylaxis injection was 1.88 (0; 3.97) for the group aged <6 years, 0 (0; 1.96) for the group aged 6–12 years, and 0 (0; 3.95) for the combined age groups. The median (Q1; Q3) annualized numbers of joint bleeds and spontaneous bleeds within the 48-hour period were both 0 (0; 0) for the combined age groups. Median (Q1; Q3) annualized number of bleeds for the combined age groups was 1.90 (0; 6.02) for total bleeds, 0 (0; 2.01) for joint bleeds, and 0 (0; 0) for spontaneous bleeds. No treatment-related serious AEs or inhibitors were reported.

Conclusion: Prophylactic treatment with BAY 81-8973 was found to be efficacious in prevention and treatment of bleeds in children with severe hemophilia A. BAY 81-8973 also exhibited good tolerability.

Disclosure of Interest: R. Ljung Consultant for: Has received consultancy and speaker fees from Bayer, Baxter, Novo Nordisk, and Octapharma, and is the global principal investigator of the LEOPOLD Kids study, G. Kenet Grant / Research Support from: BPL, Consultant for: Bayer, Baxter, Novo Nordisk and Protor, Speakers Bureau of: Advisory board member and has received honoraria for lectures from Bayer, Baxter, and Novo Nordisk, E. Santagostino Speakers Bureau of: Has received honoraria from Bayer for advisory board and speaker bureau participation, V. Kaleva: None Declared, L. Rusen: None Declared, D. Tseneklidou-Stoeter Employee of: Bayer Pharma AG, L. Michaels Employee of: Bayer HealthCare, A. Shah Employee of: Bayer HealthCare, W. Hong Employee of: Bayer HealthCare

P32 PHARMACOKINETICS OF BAY 81-8973 DURING PROPHYLACTIC TREATMENT OF PATIENTS WITH SEVERE HEMOPHILIA A IN THE LEOPOLD TRIALS
Anita Shah*, Kenetz Delesen2, Shadan Lalezari3

1Bayer HealthCare Pharmaceuticals, Whippany, NJ, United States, 2Bayer Pharma AG, Wuppertal, Germany, 3The Israel National Hemophilia Center and Thrombosis Unit, Chaim Sheba Medical Center, Tel-Hashomer, Israel

Problem Statement: BAY 81-8973 is a new full-length recombinant factor VIII (FVIII) product in development for treatment of hemophilia that has no addition of human- or animal-derived proteins during its cell culture or purification steps. A Pharmacokinetics (PK), safety, and efficacy of BAY 81-8973 were evaluated in the LEOPOLD program. The aim of the current analysis was to assess the PK of BAY 81-8973 after single and multiple dosing across ethnic groups in the 3 LEOPOLD trials and to demonstrate the PK non-inferiority of BAY 81-8973 compared with sucrose-formulated recombinant FVIII (rFVIII-FS).

Method: The LEOPOLD trials enrolled patients aged 12–65 years (LEOPOLD I and II) or ≤12 years (LEOPOLD Kids) with severe hemophilia A, ≥150 (LEOPOLD I and II) or ≥50 (LEOPOLD Kids) exposure days to any FVIII product, and no history of FVIII inhibitors. PK assessments were performed using the one-stage and chromogenic assays after a single dose of BAY 81-8973 (50 IU/kg) in LEOPOLD I and II, using the chromogenic assay only (with limited sampling) in LEOPOLD Kids, and additionally after repeated dosing in a subset of patients in LEOPOLD I. The ethnic subgroups for the PK analysis in the 3 trials included Chinese, Japanese, and non-Asian patients. The age groups for the PK sub analyses in the trials were 18–65 years, 12–17 years, 6–11 years, and ≤6 years.

Results: PK assessments based on one-stage and chromogenic assays in 26 patients in the LEOPOLD I trial showed no inferiority of BAY 81-8973 versus rFVIII-FS for all PK parameters after a single infusion. The PK after multiple BAY 81-8973 dosing in 19 patients in LEOPOLD I was similar to the PK after a single dose. Analysis of PK in the different age groups in the 3 trials showed that the maximum concentration (Cmax) and area under the curve (AUC) values for adolescents were within the range of values seen for adults; PK values were slightly lower for children compared with adults. PK analyses in the different ethnic subgroups in the 3 trials showed that the AUC and Cmax values for Chinese and Japanese patients were within the range of values seen for non-Asian patients.

Conclusion: The PK profile of BAY 81-8973 was non-inferior to rFVIII-FS. The PK results were similar following single and repeated dosing and across ethnic groups in the 3 LEOPOLD trials.

Disclosure of Interest: A. Shah Employee of: Bayer HealthCare, H. Delesen Employee of: Bayer Pharma AG, S. Lalezari Consultant for: Previously received honoraria from Bayer

P33 ANALYSIS OF CAROTID ENDOBIC STROKE SEVERITY AT ONSET AND PRIOR ANTITHROMBOTIC THERAPY
Sargylana A. Chugunova1, Andrian N. Slepctov2, Tatiana Y. Nikolaeva1

1Department of neurology, 2Department of Therapy, North-Eastern Federal University named after M.K. Ammosov (Yakutsk, Russia), Yakutsk, Russian Federation

Problem Statement: Antithrombotic therapy is used for the prevention of ischemic cardiac embolic stroke (CS) due to atrial fibrillation (AF). Anticoagulation with a vitamin K antagonist and, in special cases, aspirin is recommended for prevention of CS in patients with AF (Furie K.L. et al., 2010). Among patients who were taking warfarin, an INR < 2.0 at admission, as compared with an INR of 2.0 or greater, increased a severe stroke and the risk of death within 30 days (Hyylek E.M. et al., 2003). The aim of this study was to evaluate the onset severity of cardio embolic stroke, depending on the prior anticoagulation or antiplatelet therapy.

Method: 103 acute CS patients with AF admitted to the Regional Vascular Centre (Yakutsk) in 2013 were included in the observed group. All patients were screened including the examination of an experienced neurologist, neuroimaging (CT and / or MRI), electrocardiography, heart ultrasound, examination of cardiologist, blood coagulation tests. The presence of preceding antithrombotic therapy was identified from the information of the patient and / or relatives. Stroke severity was scored using NIHSS (National Institutes of Health Stroke Scale) at the onset of the disease before the starting of antithrombotic therapy in the hospital. Statistical analysis. Quantitative signs were described by medians (Me) and quartiles [Q1; Q3]. For comparison of the parameters of the two groups non-parametric method U-Mann-Whitney test was used.

Results: In the study group (n=103) there were 49 males (47.6%). There were 53 Caucasians (51.5%) and 50 Asians (48.5%). Mean age was 71 [64; 77] years. All patients had AF, including 100 patients with non-valvular AF (97.1%) and 3 patients with secondary AF due to the chronic rheumatic heart disease (2.9%). Permanent AF was diagnosed in 78
Right bronchial artery embolization was carried out. Multiple cavities and active bleeding inside the bigger one. Contrast revealed consolidation of the right lower lobe with an impressive cast was suctioned from the bronchial tree through the bronchoscopic channel were performed and an endotracheal tube showed that ventilation was prevented by cardiorespiratory arrest. Flexible bronchoscopy through the girl was sedated and intubated but ventilation immediately appeared to be ineffective and she had hemoptysis. Blood count, prothrombin time and partial results: A 6-year-old girl with acute lymphoblastic leukemia (cALL) developing massive hemoptysis.

Method: We report the case of a 6-year-old girl with acute lymphoblastic leukemia (cALL) developing massive hemoptysis where the use of bronchoscopy demonstrated to be a lifesaving procedure. Results: A 6-year-old girl with acute lymphoblastic leukemia was diagnosed with pneumonia of the right lower lobe. After 5 days of apyrexia she suddenly developed massive hemoptysis. Blood count, prothrombin time and partial thromboplastin time were normal. To perform bronchoscopy the girl was sedated and intubated but ventilation immediately appeared to be ineffective and she had cardiorespiratory arrest. Flexible bronchoscopy through the endotracheal tube showed that ventilation was prevented by a large quantity of clotted blood in trachea and in main stem bronchi. Repeated washing with saline solution and mucolytic through the bronchoscopic channel were performed and an impressive cast was suctioned from the bronchial tree (Image). The patient was successfully ventilated with restoration of valid heart rate and good oxygen saturation. Source of bleeding was not identified. Chest CT scan with contrast revealed consolidation of the right lower lobe with multiple cavities and active bleeding inside the bigger one. Right bronchial artery embolization was carried out.

Conclusion: Massive hemoptysis requires immediate intervention. Flexible bronchoscopy performed by skilled physicians can effectively remove large obstructing clots preventing asphyxia and preserving ventilation.

Disclosure of Interest: None declared.

### P34

**AIRWAY OBSTRUCTION BY BLOOD CLOT IN A CHILD: ROLE OF FLEXIBLE BRONCHOSCOPY**

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**Problem Statement:** In case of massive hemoptysis bronchoscopy plays a key role in localizing site of bleeding, controlling hemorrhage and clearing the airway.

**Method:** We report the case of a 6-year-old girl with acute lymphoblastic leukemia (cALL) developing massive hemoptysis where the use of bronchoscopy demonstrated to be a lifesaving procedure.

**Results:** A 6-year-old girl with acute lymphoblastic leukemia was diagnosed with pneumonia of the right lower lobe. After 5 days of apyrexia she suddenly developed massive hemoptysis. Blood count, prothrombin time and partial thromboplastin time were normal. To perform bronchoscopy the girl was sedated and intubated but ventilation immediately appeared to be ineffective and she had cardiorespiratory arrest. Flexible bronchoscopy through the endotracheal tube showed that ventilation was prevented by a large quantity of clotted blood in trachea and in main stem bronchi. Repeated washing with saline solution and mucolytic through the bronchoscopic channel were performed and an impressive cast was suctioned from the bronchial tree (Image). The patient was successfully ventilated with restoration of valid heart rate and good oxygen saturation.

Source of bleeding was not identified. Chest CT scan with contrast revealed consolidation of the right lower lobe with multiple cavities and active bleeding inside the bigger one. Right bronchial artery embolization was carried out.

**Conclusion:** Massive hemoptysis requires immediate intervention. Flexible bronchoscopy performed by skilled physicians can effectively remove large obstructing clots preventing asphyxia and preserving ventilation.

**Disclosure of Interest:** None declared.
dose. Thrombin generation was measured by Calibrated Automated Thrombogram (CAT). TGT assessments were performed on both PPP and on PRP (adjusted to final platelet count of 100,000/µL), with and without CTI. Following centrifugation and adjustment of the platelet count (where applicable), all samples were aliquoted and frozen at -80°C, according to procedures established by previous in vitro spiking experiments performed in our laboratory. Subsequently, in order to allow direct comparison of the results, all TGT samples (using all 4 assay conditions) from the same patient were analyzed simultaneously on the same microtiter plate. Either CAT reagent PPP-Low (1 pM of recombinant human tissue factor and 4 μM of phospholipid mixture, Thrombinoscope BV, Maastricht, The Netherlands) or the corresponding volume of buffer (2% BSA HEPES) was added to the PPP or PRP samples, respectively, before analysis. Both FVIIa activity levels and TGT parameters (endogenous thrombin potential [ETP], peak thrombin generation, time to peak, and lag-time) were obtained for all time points, to allow direct comparison of the FVIIa activity results with the 4 TGT assay conditions examined.

Results:
• Frozen PRP was the most sensitive method for evaluating rFVIIa activity with a good correlation observed between TGT parameters and FVIIa activity
• All TGT parameters and profiles were comparable between samples with and without CTI, for both PPP and PRP.
• Thrombin generation in PPP was less sensitive than PRP to evaluate the effect of rFVIIa treatment, having a high baseline thrombin generation and a small assessment window.
• The TGT parameters peak thrombin generation and ETP showed the best correlation with FVIIa activity levels.

Conclusions:
The preferred assay condition to evaluate rFVIIa administration using the thrombin generation assay was the use of frozen platelet rich plasma without the addition of CTI. Of the TGT parameters examined, peak thrombin generation and ETP correlated the best with FVIIa activity.
AGE AND SEX RELATED VARIATIONS IN PLATELET INDICES IN CHINESE ADULTS
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Problem Statement: The reference values of hematologic currently used in China derived from data collected for populations living in industrialized country. Ethnic origin, genetics, gender, altitude and environmental factors, especially age and sex, may influence some values. Studies suggesting that the changes of reference values for the different ages and genders may be beneficial for improved quality of healthcare. Our aim in this study was to examine platelet count, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and platelet-large cell ratio (P-LCR) in healthy Chinese adults and the relationship with age and sex.

Method: In the present study, we performed a retrospective analysis on 46872 local healthy individuals aged>18yrs and the mean age of patient group was 41.71 and male to female ratio was 27543:19329. Platelet indices were measured within 2hrs from blood collection and of K3 salt of ethylenediaminetetraacetic acid (EDTA) anti-coagulated at 8 00–9 00 a.m. All the tests were performed on XN-9000 (Sysmex, Japan) hematological analyzer. The significance of differences between age and gender were assessed by one way analysis of variance (ANOVA). Correlation was assessed by the Pearson’s correlation coefficient(r). Statistical analyses were performed with SPSS19.0 software (Chicago, IL) and Excel 2007. Statistical significance was set at P<0.05. Data were reported as mean and 95% confidence interval (CI).

Results: The distribution of platelet count and PCT by age and sex shows a slow, progressive decline with aging in both males and females. On average, a 10-year increase in age corresponds to an average of 9×10^9/L decrease in platelet count, adjusting for sex (P<0.001). However, in the very old people (>81yrs), there were an increasing trend in both platelet count and PCT. A strong, negative correlation between these two indices with aging was observed (Spearman’s rank correlation coefficient =−0.69, P=0.034). On the contrary, the distribution of MPV, PDW and P-LCR by age and sex shows a slow, progressive increasing trend with aging in both males and females. Interesting, in the very old people (>71yrs), there were a decreasing trend in MPV, PDW and P-LCR. A positive correlation between these three indices with aging was observed. It’s very interest that mean platelet count in Chengdu China were lower than other countries and the MPV values in our study was found to be higher than all the results reported as yet.

Image:

Conclusion: These findings suggest that the platelet indices could be greatly influenced in healthy subjects by age and sex. Based on this findings, it would be reasonable to conduct formal prospective studies to determine the clinical significance of these differences and to explore the effects of genetic background on these indices. Further studies would be necessary to make additional verifications.

Disclosure of Interest: None Declared
Congress on Controversies in Thrombosis & Hemostasis

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Industry Symposium
Saturday, November 1, 2014

08:30-10:00  BAYER SATELLITE SYMPOSIUM: EVIDENCE AND PERCEPTIONS IN HEMOPHILIA TREATMENT

Chairperson:  P.M. Mannucci, Italy

08:30-08:35  Introduction  
            P.M. Mannucci, Italy

08:35-09:00  Advances in the development of new short-acting therapies
            R. Klamroth, Germany

09:00-09:25  Emerging long-acting therapies: State of the art
            P.M. Mannucci, Italy

09:25-09:50  Debate: Will long-acting replace short-acting as the standard of care?
            P. Giangrande, UK
            C. Kessler, USA

09:50-10:00  Summary, discussion and Q&A
            P.M. Mannucci, Italy

This session is not included in the CME/CPD credit program
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