How to approach a patient with bleeding?

ISTH Advanced training course, Portugal March 2014
Differential diagnosis

bleeding

- Hemophilia
- vWD
- Platelet disorders
- liver failure
- factor deficiencies
- hyperfibrinolysis
- TIC
- anticoagulant treatment
Clinical situations

suspected bleeding disorder

w/o acute bleeding

acute bleeding
Clinical situations

suspected bleeding disorder

w/o acute bleeding

acute bleeding
Initial question

Suspected bleeding disorder

bleeding disorder likely or unlikely?
Initial work-up (I)

Suspected bleeding disorder

bleeding history

bleeding disorder likely or unlikely?
Bleeding history

- type and frequency of bleeding
- provoked or unprovoked
- type of treatment
- family history (family tree)
- drug history
Bleeding history

- usually clear in patients with severe bleeding disorders

- in patients with mild/moderate bleeding symptoms a standardized questionnaire is helpful

- standardized scores to quantitate bleeding symptoms
# Bleeding history: scoring key

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>no/trivial &lt; 5/y</td>
<td>&gt; 5/y</td>
<td>Packing/cauterization</td>
<td>transfusion, replacement, DDAVP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>no/trivial &lt; 1 cm</td>
<td>&gt; 1 cm w/h trauma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minor wounds</td>
<td>no/trivial &lt; 5/y</td>
<td>&gt; 5/y or &gt; 5 min</td>
<td>Surgical hemostasis</td>
<td>Hemostatic treatment</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>no</td>
<td>Reported at least 1</td>
<td>Surgical hemostasis</td>
<td>Hemostatic treatment</td>
</tr>
<tr>
<td>Gastro-intestinal tract</td>
<td>no</td>
<td>Identified cause</td>
<td>Surgical hemostasis</td>
<td>Hemostatic treatment</td>
</tr>
</tbody>
</table>
## Bleeding history: scoring key

<table>
<thead>
<tr>
<th>Symptom</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth extraction</td>
<td>No bleeding in 2</td>
<td>None done or no bleeding in 1</td>
<td>reported</td>
<td>Resuturing, repacking or antifibrinolytics</td>
<td>Transfusion, replacement, DDAVP</td>
</tr>
<tr>
<td>Surgery</td>
<td>No bleeding in 2</td>
<td>None done or no bleeding in 1</td>
<td>reported</td>
<td>Surgical hemostasis or antifibrinolytics</td>
<td>Transfusion, replacement, DDAVP</td>
</tr>
<tr>
<td>Muscle hematoma</td>
<td>-</td>
<td>never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous requiring treatment</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>-</td>
<td>never</td>
<td>Post-trauma, no therapy</td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>CNS</td>
<td>-</td>
<td>never</td>
<td>-</td>
<td>-</td>
<td>Subdural, intracerebral</td>
</tr>
</tbody>
</table>
Validated questionnaire¹,²

- includes 13 bleeding symptoms
- provides a summative score
- mean bleeding scores:
  in healthy individuals: 0.5
  abnormal: ≥ 2

¹Biss TT, et al. J Thromb Haemost 2010; 8: 950
²Biss TT, et al. J Thromb Haemost 2010; 8: 1416
Initial work up (II)

Suspected bleeding disorder

- bleeding history
- physical examination
Physical examination

- inspection for any bleeding signs
- joint abnormalities
- lymphadenopathy
- organomegalies
- in children: signs of nonaccidental trauma!
Initial work up (III)

Suspected bleeding disorder

- bleeding history
- physical examination
- laboratory screening

?
Decision pathway (I)

Suspected bleeding disorder

bleeding history: normal

physical examination: no signs of bleeding

laboratory screening not recommended
Take home message (I)

- Thorough personal and family histories are the best screening tests for identifying potential hemostatic problems.

- Properly obtained histories eliminate the need for laboratory screening procedures.
Suspected bleeding disorder

bleeding history: abnormal

physical examination: signs of bleeding

bleeding disorder possible/likely

laboratory screening recommended
Screening parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (males)
FXIII

CBC, complete blood count; PBF, peripheral blood film; PFA, platelet function analyser; PT, prothrombin time; APTT, activated partial thromboplastin time
Screening parameters

- bleeding disorder possible/likely
- CBC/PBF/PFA
- PT/APTT
- FVIII (male patient)
- FXIII
CBC/PBF/PFA

CBC/PBF:
- platelet count, size and morphology
- leukocyte morphology
- other cytopenias

PFA:
- axis subendothelium-vWF-platelet
- platelet-platelet interaction
Platelet function analyser (PFA)
CBC/PBF/PFA: pitfalls

CBC:
- pseudothrombocytopenia

PFA:
- hematocrit < 35
Pseudothrombocytopenia

- EDTA-induced agglutination of platelets
- w/o clinical relevance
- confirmed by platelet counting using citrate anticoagulated blood

ASH et al. Blood 2011;117:4168-4168
Decision finding (III)

- **platelet count** > 150,000/µl
- blood smear: normal
  - PFA normal
  - **platelet disorder/vWD unlikely**
Decision finding (IV)

Abnormal platelet morphology → Platelet disorder likely
DD: Platelet disorder

- **mean platelet volume**
  - **< 6 fl**
    - micro platelets
      - Wiskott-Aldrich-syndrome/XLT
  - **7 - 11 fl**
    - DD: granule disorders/GT
  - **> 15 fl**
    - giant platelets
      - DD: BSS/MYH9-related disorders
Confirmatory procedures

abnormal platelet morphology

platelet disorder likely

aggregation/secretion
flow cytometry
 genetic testing
Decision finding (V)

- **platelet count:** < 100,000/µl

  - **blood smear/mean platelet volume:** normal

  - **quantitative platelet disorder likely**
Isolated thrombocytopenia

- Synthesis ↓
- Consumption ↑
- Degradation ↑

Low platelet count
Isolated thrombocytopenia

- BM-failure
  - synthesis ↓

- infection/DIC
  - consumption ↑

- splenomegalie/immune response
  - degradation ↑

→ low platelet count
Additional information

- isolated versus combined
- new onset or chronic
- signs of organomegalie
- drug history
- previous infections
Additional information

- isolated versus combined

- new onset or chronic

- no signs of organomegalie

- no drug intake

- previous infections

⇒ immune thrombocytopenia suspected
Decision finding (VI)

- platelet count > 150,000/µl
  - blood smear: normal
    - PFA abnormal
      - vWD suspected
Confirmatory procedures

vWD suspected

AB0 blood group
vWF antigen
Ristocetin Cofactor
collagen binding assay
FVIII testing
Confirmatory procedures

vWD suspected

AB0 blood group
vWF antigen
Ristocetin Cofactor collagen binding assay
FVIII testing

genetic testing
vWF-multimeric analysis
propeptide analysis
Screening parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (male patient)
FXIII
DD: single factor deficiencies

- **PT**
  - prolonged
    - APTT
      - normal
        - FVII
      - prolonged
        - FX/FV/FII fibrinogen
    - prolonged
      - HK/PK/FXII FXI FIX FVIII
  - normal
    - APTT
      - factor deficiency unlikely except FXIII
Screening parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (male patient)
FXIII
Hemophilia A pattern

- **PT: 12 s (10.7-12.9s)**
  - prolonged
    - **APTT**
      - normal
        - FVII
      - prolonged
        - FX/FV/FII fibrinogen
    - prolonged
      - HMWK
      - PKK
      - FXII
      - FXI/FIX
      - FVIII: 3%
  - normal
    - APTT: 80s (25-35s)
    - factor deficiency unlikely except FXIII
APTT versus FVIII (one stage)

- aPTT (s)
- FVIII activity (%)

- Healthy volunteers
- Hemophiliac patients

25.5 - 34.3 s
48 - 124 %
Screening parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (male patient)
FXIII
Confirmatory procedures

- hemophilia A suspected
  - amidolytic FVIII
  - two-stage FVIII
  - TGA
  - vWD type N
  - genetic testing
DD: single factor deficiencies

PT: normal

APTT: prolonged

FXI/FIX/FVIII: normal

contact factor deficiency suspected
Confirmatory procedures

- contact factor deficiency suspected
  
  single factor analysis: HK/PK/FXII
  
  contact factor deficiency: clinically not relevant except ACT-/APTT-monitoring
## Patients: initial screens

<table>
<thead>
<tr>
<th>Patient</th>
<th>Platelet count (/µl)</th>
<th>PT (s)</th>
<th>APTT (s)</th>
<th>FXIII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>234,000</td>
<td>61</td>
<td>&gt; 150</td>
<td>89</td>
</tr>
<tr>
<td>#2</td>
<td>172,000</td>
<td>11</td>
<td>&gt; 150</td>
<td>91</td>
</tr>
</tbody>
</table>
DD: single factor deficiencies

- **PT**
  - prolonged
    - **APTT**
      - normal
        - **FVII**
        - **patient #1**
      - prolonged
        - **FX/FV/FII fibrinogen**
        - **patient #2**
    - prolonged
      - **HMWK PKK FXII FXI/FIX/FVIII**
      - factor deficiency unlikely except FXIII
  - normal
    - **APTT**
      - normal
        - **FXIII**
Patients: single factor analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>FII (%)</th>
<th>FX (%)</th>
<th>FV (%)</th>
<th>FIX (%)</th>
<th>FVIII (%)</th>
<th>FXI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>87</td>
<td>2</td>
<td>89</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>#2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>83</td>
<td>&lt;1</td>
<td>91</td>
</tr>
</tbody>
</table>

Suspected diagnosis:
Patient #1: FX deficiency
Patient #2: FVIII deficiency (severe hemophilia)
Patient #1: 68-y old male

- severe hematoma after minimal trauma

- he reported no personal or familial history of bleeding
Patient #2: 56-y old male

- severe postoperative bleeding after hernia operation

- haematothorax after central venous support

- massive transfusion 24 RBC, 32 FFP 4 platelet conc.

- referred to Bonn via helicopter
Acquired hemophilia

- large hematomas
- extensive ecchymoses
- severe mucosal bleeding
- gastrointestinal bleeding
- gross hematuria
- w/o a bleeding history
Laboratory approach

inhibitor suspected

inhibitor screen (mixing test)
Inhibitor screen

- Patient plasma is mixed with increasing concentrations of normal human plasma

- Clotting factor activity measured after incubation for 1 and 2 hours at 37°C
Inhibitor screen: negative
Inhibitor screen: positive
## Patients: inhibitor screen

<table>
<thead>
<tr>
<th>Patient</th>
<th>FX (%)</th>
<th>FV (%)</th>
<th>FVIII (%)</th>
<th>Mixing test</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2</td>
<td>89</td>
<td>-</td>
<td>neg</td>
</tr>
<tr>
<td>#2</td>
<td>-</td>
<td>-</td>
<td>&lt;1</td>
<td>pos</td>
</tr>
</tbody>
</table>
Laboratory approach

inhibitor screen (mixing test) positive

inhibitor quantification
Serial dilutions of patient plasma are incubated for two hours at 37°C with normal human plasma.

Factor activity is then measured using a clotting assay.

1 Bethesda unit (BU) is defined to reduce the activity of a clotting factor in normal human plasma to 50%.
Bethesda units (BU)
## Patients: Bethesda units (BU)

<table>
<thead>
<tr>
<th>Patient</th>
<th>FX (%)</th>
<th>FV (%)</th>
<th>FVIII (%)</th>
<th>Mixing test</th>
<th>BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2</td>
<td>89</td>
<td>-</td>
<td>neg</td>
<td>-</td>
</tr>
<tr>
<td>#2</td>
<td>-</td>
<td>-</td>
<td>&lt;1</td>
<td>pos</td>
<td>37</td>
</tr>
</tbody>
</table>
Patient #2: 56-y old male

- severe postoperative bleeding after hernia operation

- haematotherax after central venous support

→ acquired hemophilia A caused by high titer FVIII-autoantibodies
## Acquired inhibitors: frequencies

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Estimated frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>$1 - 1.5 \times 10^6$ in non-hemophiliacs</td>
</tr>
<tr>
<td>Factor II</td>
<td>few case reports only</td>
</tr>
<tr>
<td>Factor V</td>
<td>$\sim 105$ cases described</td>
</tr>
<tr>
<td>Factors VII, IX, X, XI</td>
<td>few case reports only</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>$\sim 20$ cases described</td>
</tr>
</tbody>
</table>
## Patients: inhibitor screen

<table>
<thead>
<tr>
<th>Patient</th>
<th>FX (%)</th>
<th>FV (%)</th>
<th>FVIII (%)</th>
<th>Mixing test</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2</td>
<td>89</td>
<td>-</td>
<td>neg</td>
</tr>
<tr>
<td>#2</td>
<td>-</td>
<td>-</td>
<td>&lt; 1</td>
<td>pos</td>
</tr>
</tbody>
</table>
The majority of acquired inhibitors are antibodies that either inhibit the activity or increase the clearance of a clotting factor.
Laboratory approach

inhibitor suspected

inhibitor screen negative

screen for precipitating antibodies
Acquired inhibitor: ELISA

\[ \alpha \text{-IgG/M} \]

purified clotting factor

microtiter plate
## Patients: laboratory data

<table>
<thead>
<tr>
<th>Patient</th>
<th>FX (%)</th>
<th>FV (%)</th>
<th>Mixing test</th>
<th>BU</th>
<th>APA</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2</td>
<td>89</td>
<td>neg</td>
<td>-</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>#2</td>
<td>-</td>
<td>-</td>
<td>pos</td>
<td>37</td>
<td>neg</td>
<td>-</td>
</tr>
</tbody>
</table>
Patient #1: 68-y old male

- severe hematoma after minimal trauma
- skin biopsy reveals amyloidosis

→ amyloid-associated FX-deficiency
Screening parameters

bleeding disorder possible/likely

CBC/PBF/PFA
PT/APTT
FVIII (male patient)
FXIII

normal?
Extended screening

bleeding disorder possible/likely

initial screen: normal

$\alpha_2$-antiplasmin
platelet function testing/vWF-testing
vascular bleeding disorder
repeat testing during active bleeding
Clinical decision finding

bleeding disorder possible/likely

extended screening w/o abnormal results

suspected diagnosis: bleeding disorder of unknown reason
Take home message (II)

- If relatively simple screening procedures are used, the vast majority of hemorrhagic problems can be identified.

- Confirmatory tests are subsequently used to establish an appropriate differential diagnosis.
Clinical situations

- suspected bleeding disorder
  - w/o acute bleeding
  - acute bleeding
Acute Bleeding: Grading

- Life-threatening (WHO grade 4) 
  **Trauma** or critical organ bleeding

- Severe (WHO grade 3) 
  gross blood loss, requires transfusion

- Mild blood loss but clinically significant 
  (WHO grade 2)
TIC-cascade (I)

- Severe trauma
  - Massive blood loss
    - Loss of clotting factors/platelets
      - Coagulopathy
TIC-cascade (II)

Severe trauma

- Massive blood loss
- Activation of the coagulation system
- Consumption of clotting factors/platelets
  - Thrombin burst
  - Coagulopathy

Loss of clotting factors/platelets
Severe trauma leads to massive blood loss and consumption of clotting factors/platelets, activation of the coagulation system, and thrombin burst. This results in generation of APC and systemic anticoagulation, leading to coagulopathy.
TIC: APC-formation

C = control, T = trauma, H = hemorrhage, TH = trauma + hemorrhage

severe trauma

massive blood loss

loss of clotting factors/platelets

hypoperfusion/anoxia

activation of the coagulation system

consumption of clotting factors/platelets

thrombin burst

generation of APC

systemic anticoagulation

coagulopathy
t-PA-secretion

- thrombin
- acidosis
- PAR?

- epinephrin
- prostacycline
- vasopressin
- V₂-R ?

Ca²⁺↑

cAMP↑

t-PA/PAI

t-PA: tissue-type plasminogen activator
TIC-cascade (V)

Severe trauma

- Massive blood loss
  - Loss of clotting factors/platelets
  - Hypoperfusion/anoxia
    - PA-release from ECs
      - Hyperfibrinolysis

- Activation of the coagulation system
  - Consumption of clotting factors/platelets
  - Thrombin burst
    - Generation of APC
      - Systemic anticoagulation

Coagulopathy
TIC: treatment options

- Severe trauma
  - Massive blood loss
    - Loss of clotting factors/platelets
    - Hypoperfusion/anoxia
      - PA-release from ECs
        - Hyperfibrinolysis
  - Activation of the coagulation system
    - Consumption of clotting factors/platelets
      - Thrombin burst
        - Generation of APC
          - Systemic anticoagulation
            - Coagulopathy

- Surgery
TIC: treatment options

Severe trauma

- Massive blood loss
  - Hypoperfusion/anoxia
    - PA-release from ECs
      - Hyperfibrinolysis
- Activation of the coagulation system
  - Thrombin burst
    - Generation of APC
      - Systemic anticoagulation

Surgery

- Loss of clotting factors/platelets
- TXA
- FFP?
- Transfusion

Transfusion

Coagulopathy
Tranexamic acid (TXA)
**CRASH-2 trial**

<table>
<thead>
<tr>
<th>Study population:</th>
<th>20,211 trauma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group:</td>
<td>1 g TXA bolus/1 g over 8 h</td>
</tr>
<tr>
<td>Control group:</td>
<td>Placebo</td>
</tr>
<tr>
<td>All-cause mortality:</td>
<td>14.5% vs. 16% (p = 0.0035)</td>
</tr>
<tr>
<td>Bleeding related mortality:</td>
<td>4.9% vs. 5.7%</td>
</tr>
</tbody>
</table>

TIC: treatment triggers

1. Clinical probability of TIC

1. Laboratory values
High TIC risk: indicators*

- hemorrhagic shock on admission
- pelvic fracture/multiple bone fractures
- rupture of liver/spleen/positive FAST
- brain damage
- BE < -6
- use of antithrombotic drugs

* TASH-Score, German Society of Trauma Surgeons
TIC: hemostatic support (I)

severe trauma

TIC-risk: high

TXA 1g Bolus followed by 1g/h¹

hemostasis screen: CBC/PT/APTT/fibrinogen

¹CRASH-2 trial. Lancet 2010; 376: 23-32, TXA: tranexamic acid
TIC: hemostatic support (II)

High TIC risk?

- yes
  - 3g fibrinogen
  - FFP/PRC 1:1

- no
  - parameter-adjusted treatment
Parameter-adjusted treatment

Fibrinogen:
- < 1.5 g/dl with ongoing blood loss/ICB
- < 0.5 g/dl
→ 3 g fibrinogen concentrate

Prothrombin time:
- > 25s with ongoing blood loss/ICB
- < 50s
→ 50 IE/kg b.w. PCC

ICB, intracranial bleeding;
Parameter-adjusted treatment

→ platelet transfusion, if platelet count:

- < 100,000/µl with ongoing bleeding/ICB
- < 50,000/µl with coagulopathy
- < 30,000/µl

ICB, intracranial bleeding
Parameter-adjusted treatment

Signs of hyperfibrinolysis

→ bolus injection of 1 g TXA followed by 20 mg/kg b.w./h

→ 3 g fibrinogen concentrate
TEG: fibrinolysis

time axis

max. amplitude

r-time  k-time
Take home message (III)

- TIC is frequent in severe trauma patients.

- TIC is caused by consumption and loss of coagulation factors and platelets and by secondary hyperfibrinolysis and APC formation.

- TIC can be successfully treated by TXA treatment and transfusion of blood products including fibrinogen, fresh frozen plasma and platelets.
Acute Bleeding: Grading

- Life-threatening (WHO grade 4)
  Trauma or critical organ bleeding

- Severe (WHO grade 3)
  gross blood loss, requires transfusion

- Mild blood loss but clinically significant (WHO grade 2)
Critical organ bleeding

Suspected anticoagulant treatment

antithrombotic screen:
APTT/INR/TT/BT/aFXa/TTI

*APTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time; BT, batroxabbin time; aFXa, anti-FXa-activity; TTI, thrombin inhibition time*
## Anticoagulant screen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result indicating a clinically relevant anticoagulant activity</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH/ Fondaparinux</td>
<td>Argatroban Bivalirudin Dabigatran</td>
</tr>
<tr>
<td>APTT</td>
<td>normal</td>
<td>prolonged</td>
</tr>
<tr>
<td>INR</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>TT</td>
<td>normal</td>
<td>prolonged</td>
</tr>
<tr>
<td>BT</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>aFXa</td>
<td>detectable</td>
<td>not detectable</td>
</tr>
<tr>
<td>TTI</td>
<td>no inhibition</td>
<td>inhibition</td>
</tr>
</tbody>
</table>
# Anticoagulant screen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result indicating a clinically relevant anticoagulant activity</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH/ Fondaparinux</td>
<td>Argatroban Bivalirudin Dabigatran</td>
</tr>
<tr>
<td>APTT</td>
<td>normal</td>
<td>prolonged</td>
</tr>
<tr>
<td>INR</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>TT</td>
<td>normal</td>
<td>prolonged</td>
</tr>
<tr>
<td>BT</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>aFXa</td>
<td>detectable</td>
<td>not detectable</td>
</tr>
<tr>
<td>TTI</td>
<td>no inhibition</td>
<td>inhibition</td>
</tr>
</tbody>
</table>
## Anticoagulant screen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result indicating a clinically relevant anticoagulant activity</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH/Fondaparinux</strong></td>
<td><strong>Argatroban</strong> prolonged, <strong>Bivalirudin</strong> normal, <strong>Dabigatran</strong> prolonged</td>
<td>prolonged</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td><strong>INR</strong> normal, <strong>Argatroban</strong> increased, <strong>VKA</strong> increased, <strong>Rivaroxaban</strong> increased</td>
<td>increased</td>
</tr>
<tr>
<td><strong>TT</strong></td>
<td><strong>TT</strong> normal, <strong>Argatroban</strong> prolonged</td>
<td>normal</td>
</tr>
<tr>
<td><strong>BT</strong></td>
<td><strong>BT</strong> normal, <strong>Argatroban</strong> normal</td>
<td>normal</td>
</tr>
<tr>
<td><strong>aFXa</strong></td>
<td>detectable, <strong>Argatroban</strong> not detectable, <strong>VKA</strong> not detectable, <strong>Rivaroxaban</strong> detectable</td>
<td>detectable</td>
</tr>
<tr>
<td><strong>TTI</strong></td>
<td>no inhibition, <strong>Argatroban</strong> inhibition</td>
<td>no inhibition</td>
</tr>
</tbody>
</table>
Take home message (IV)

- If six relatively simple screening procedures are used, patients showing clinically relevant plasma levels of anticoagulants can be identified.