What should the anaesthesiologist know about the inherited bleeding disorders

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Disclosure

- I received in the past travel grants and speaker fees from Bayer, GSK, Novo-Nordisk, Pfizer and Sanofi-Aventis

- Co-author of 2013 European Guidelines on management of the trauma bleeding patients – unrestricted grant from CLS Behring and LFB France

- Co-author of 2013 ESA Guidelines on management of the severe perioperative bleeding
Case presentation

42-year-old man, 64 kg weight
Moderate haemophilia: Fc VIII 5%
Spontaneous bleeding episodes (nasal)
Haemophilic arthropathy - knees and elbows
Orthopedic surgery (14 yrs ago): wedge osteotomy with metal plate and screws
Perioperative Fc VIII replacement therapy; No inhibitors
Scheduled for CABG surgery
Perioperative Factor VIII levels and Fc VIII replacement (surgery and day 0)

Surgery (total OR time = 6 hrs)

- 8:00: 4000 IU ReFacto bolus
- 10:00: 2000 IU ReFacto bolus
- 10:00: Heparin 25,000 IU
- 13:00: Protamine 250 mg
- 16:00: Tranexamic acid (7 g)
- 7:00: Heparin 300 IU/h

VIII FC Level (%)
Postoperative Factor VIII levels and Fc VIII replacement (day 1-day 10)

- Day 0: 17:00
- Day 1: 07:00, 15:00
- Day 2: 07:00, 13:00
- Day 3: 07:00, 15:00
- Day 4
- Day 5
- Day 6: 07:00
- Day 7: 07:00, 15:00, 10:00
- Day 8: 07:00
- Day 9: 08:00
- Day 10: 07:00

VIII Fc Level (%)

Key events:
- 2000 IU ReFACTO bolus
- Chest tube, arterial catheter, CVC removed
- Transfer from ICU to ward
- Pacer wires removed
- Heparin
- Clopidogrel

Postop. days
Re admission - late cardiac tamponade
(pericadial clot with compression of right atrium, SVC and IVC)

TTE, apical 4 chambers- extrinsec compression of right atrium
Postoperative evolution

CABG

- Transfer to ward
- Pacer wires removed

Discharged from hospital

Re admission

- Clot removal
- Hematology department

- Discharged from hospital

28,000 IU ReFACTO

76,500 IU ReFACTO
Inherited bleeding disorders

N = 489

- disorders of primary haemostasis
  - Von Willebrand disease
    - VWF ↓
  - Other coagulation disorders
    - (eg, VII↓, XI ↓)

- disorders of secondary haemostasis
  - Haemophilia A
    - VIII↓
  - Haemophilia B
    - IX↓

- Inherited thrombocytopenias
  - 10%

- Miscellaneous (eg, Elhers-Danlos syndrome)
  - 4%

- Platelet function disorders
  - 35%

Modified from www.bloodcmecenter.org
Image courtesy of Victor S. Blanchette, MD, FRCP
Bleeding Severity, Diagnostic Difficulty, and Prevalence of Inherited Bleeding Disorders

- Glanzmann, Bernard-Soulier, VWD variants, Severe Hemophilias
- Type 1 VWD with VWF ≤30%
- Most Type 1 VWDs, Mild Platelet Function Disorders, Clotting Factor Deficiencies
- Bleeding of undefined cause

von Willebrand disease

von Willebrand factor

- Synthesis in endothelium and megakaryocytes
- Forms large multimers
- Carrier of factor VIII
- Anchors platelets to subendothelium
- Bridge between platelets

# VWD - Classification

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Mechanism of Disease</th>
<th>Genetic Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of von Willebrand factor (and factor VIII)</td>
<td>Autosomal dominant*</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative defects of von Willebrand factor</td>
<td>Autosomal dominant†</td>
</tr>
<tr>
<td>A</td>
<td>Defective platelet-dependent von Willebrand factor functions, associated with lack of larger multimers</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Heightened platelet-dependent von Willebrand factor functions, associated with lack of larger multimers</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Defective platelet-dependent von Willebrand factor functions, not associated with multimer defects</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Defective von Willebrand factor binding to factor VIII</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe or complete deficiency of von Willebrand factor and moderately severe factor VIII deficiency</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

From: Mannucci PM. NEJM 2004: 683-694
## VWD - Clinical manifestations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>50</td>
</tr>
<tr>
<td>Surgery-related</td>
<td>50</td>
</tr>
<tr>
<td>Dental-related</td>
<td>50</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>80</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>80</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>30</td>
</tr>
</tbody>
</table>

Images from [www.bloodcmecenter.org](http://www.bloodcmecenter.org)
Low von Willebrand factor: sometimes a risk factor and sometimes a disease

J. Evan Sadler

ASH Education Book 2009;1:106-112
Treatment of VWD

- Endogenous VWF release by desmopressin
- Replacement therapy with VWF containing plasma-derived products
- Promoting haemostasis with antifibrinolytics and platelet transfusion
Synthetic analog of vasopressin
- Acts on $V_2$ receptors: induces an increase (3-5 x) in plasma levels of VWF and FVIII
- First choice treatment of type 1 VWD, variable effective in type 2, ineffective in type 3

Desmopressin – dose and monitoring

• 0.3 μg kg⁻¹ in 30–50 mL of normal saline given over 30 min. and repeated every 12 to 24 hours, generally 2-4 doses

• Peak increases in VWF and FVIII are observed between 30 and 90 min after infusion

• A test-infusion should be given to all patients with clinically relevant VWD

From: Federici AB et al. Hemophilia 2008, 14(Suppl. 1): 5-14
VWD - replacement therapy

- Plasma derived factors containing VWF (pd-VWF)
- Fresh frozen plasma (FFP)
- Cryoprecipitate (CP)
Haemostatic components of cryoprecipitate and FFP

<table>
<thead>
<tr>
<th>Component</th>
<th>Cryoprecipitate (per mL)</th>
<th>FFP (per mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXIII activity, U</td>
<td>2.8 ± 1.5</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>FXIII antigen, mg</td>
<td>0.031 ± 0.01</td>
<td>0.0096 ± 0.003</td>
</tr>
<tr>
<td>FVIII activity, U</td>
<td>6.3 ± 1.9</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Fibrinogen, mg</td>
<td>8.8 ± 2.6</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>vWF:Ag, U</td>
<td><strong>8.6 ± 2.7</strong></td>
<td><strong>0.9 ± 0.2</strong></td>
</tr>
<tr>
<td>vWF:RCo, U</td>
<td><strong>8.0 ± 1.8</strong></td>
<td><strong>0.9 ± 0.2</strong></td>
</tr>
<tr>
<td>Bag volume, mL</td>
<td>21.3 ± 2.7</td>
<td>245 ± 29</td>
</tr>
</tbody>
</table>

Modified from: Caudil J et al. Transfusion 2009;49:765
# Treatment of von Willebrand disease with FVIII/VWF concentrates

Giancarlo Castaman

## Table I - FVIII/VWF concentrates available in Italy for VWD treatment.

<table>
<thead>
<tr>
<th>Product</th>
<th>Purification</th>
<th>Viral inactivation</th>
<th>Specific activitya (U/mg protein)</th>
<th>VWF:RCo/Ag (ratio)</th>
<th>VWF:RCo FVIII:C (ratio)</th>
<th>Other proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphanate</td>
<td>Affinity chromatography (heparin)</td>
<td>Solvent/detergent + 72 h at 80 °C</td>
<td>&gt;100</td>
<td>0.94</td>
<td>1.21</td>
<td>Albumin +</td>
</tr>
<tr>
<td>(Grifols, Los Angeles, USA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanhdi</td>
<td>Affinity chromatography (heparin)</td>
<td>Solvent/detergent + 72 h at 80 °C</td>
<td>&gt;100</td>
<td>0.83</td>
<td>1.48</td>
<td>Albumin +</td>
</tr>
<tr>
<td>(Grifols, Barcelona, Spain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemate® P</td>
<td>Multiple precipitation</td>
<td>Pasteurisation 10 h at 60 °C</td>
<td>40±6</td>
<td>0.96</td>
<td>2.54</td>
<td>Albumin +</td>
</tr>
<tr>
<td>(CSL Behring, Marburg, Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunate</td>
<td>Ion exchange chromatography</td>
<td>Detergent + vapour heat 10 h at 60 °C, 1 h at 80 °C</td>
<td>100±50</td>
<td>0.47</td>
<td>1.10</td>
<td>Albumin +</td>
</tr>
<tr>
<td>(Baxter, Wien, Austria)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilfactin</td>
<td>Aluminium hydroxide gel adsorption ion exchange + Affinity chromatography</td>
<td>Solvent/detergent; dry heat; 72 h at 80 °C; 35 nm nanofiltration</td>
<td>≥50*</td>
<td>0.95</td>
<td>&gt;10</td>
<td>Albumin +</td>
</tr>
</tbody>
</table>
Products with a VWF/FVIII ratio >1 should be preferred

Patients undergoing elective surgery should receive a concentrate infusion a couple of hours before the procedure in order to allow enough time for new synthesis of endogenous FVIII

In emergency situations, VWF concentrates containing large quantities of FVIII may be preferred to accelerate the effect of haemostasis

Supernormal levels of VWF/FVIII may increase the thromboembolic risk

## Recommendations of peri-procedural replacement therapy

<table>
<thead>
<tr>
<th>Type of haemorrhage</th>
<th>Target levels of VWF/ FVIII (IU/dL)</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initial</td>
<td>Subseq.</td>
</tr>
<tr>
<td>Major surgery</td>
<td>100</td>
<td>&gt; 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor surgery</td>
<td>&gt; 30-50</td>
<td>&gt; 30-50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic procedures</td>
<td>&gt; 50</td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Managing Patients with von Willebrand Disease Type 1, 2 and 3 with Desmopressin and von Willebrand Factor-Factor VIII Concentrate in Surgical Settings

Jan Jacques Michiels\textsuperscript{a,c} Huub H.D.M. van Vliet\textsuperscript{b} Zwi Berneman\textsuperscript{a} Wilfried Schroyens\textsuperscript{a} Alain Gadisseur\textsuperscript{a}


250-300 IU/dL
200 IU/dL
1990-2011
71 prospective studies
5528 patients
27 different concentrates

20 thrombotic adverse events (3.6 per 10³ patients)
2 major thromboses (3.6 per 10⁴ patients) both in VWD
Inherited platelet defects
Inherited platelet defects

- Mild to moderate muco-cutaneous bleeding tendency (echimosis, petechia, purpura, gingival)
- No deep tissue bleeding or haemarthroses
- Could present particularly abundant bleeding after surgery, trauma or invasive procedures

Images from www.bloodcmecenter.org
Courtesy by David Green, eAtlas of Pathology, and Peter A. Kouides
**Inherited severe platelet defects**

**Bernard-Soulier syndrome** is due to dysfunction or absence of a platelet membrane receptor (GP Ib/IX/V) resulting in abnormal adhesion of platelets to subendothelial-bound von Willebrand factor during the formation of platelet plug.

**Glanzmann thrombasthenia** is characterized by a deficiency or functional defect of platelet GP IIb/IIIa resulting in abnormal aggregation.

Alamelu J & Liesner R. Brit J Haematol 2010;813-829
Inherited platelet defects - therapy

- Desmopressin
- Antifibrinolytics
- Platelet transfusion
- Recombinant factor VIIa

Alamelu J & Liesner R. Brit J Haematol 2010;813-829
Seligsohn U. Haemophilia 2012;18:161-165
A practical concept for preoperative management of patients with impaired haemostasis

Tranexamic acid partially improves platelet function in patients treated with dual antiplatelet therapy
Evidence supporting the use of recombinant activated factor VII in congenital bleeding disorders

Pär I Johansson
Sisse R Ostrowski

rFVIIa is licensed for thrombasthenia Glanzmann

No RCTs in patients with congenital platelet defects!
Platelet transfusion

To reduce the risk of allo-immunization and the risk of refractoriness:

- HLA and ABO-matched donors
- leucodepleted blood components
- apheresis units from single donors
Disorders of secondary hemostasis

• **Haemophilia A**
  • deficit of F VIII
  • prevalence 1/10 000 male births

• **Haemophilia B**
  • deficit of F IX
  • prevalence 1/60 000 male births

Sex-linked disease affecting males
Reported prevalence varies among countries

Negrier C. Hemophilia A. [www.orpha.net](http://www.orpha.net) 2011
Factor VIII or IX levels and severity of haemophilia

Severe   < 1%

Moderate 1-5%

Mild  6-24%

25-49%

50-150%

> 150%

Guidelines for the Management of Hemophilia p. 8, Table 1.1, www.wfh.org
Martlew VJ. Peri-operative management of patients with coagulation disorders. BJA 2000 Sep; 85 (3):446-55. PubMed PMID:11103188
The ‘royal disease’— haemophilia A or B? A haematological mystery is finally solved

From: Heremans LN. Haemophilia 2010;16: 833-847
Lack of excessive hemorrhage from minor cuts or abrasions, due to normal platelet function
A major bleed about 20 times/year

✧ Haemarthrosis
✧ Haemorrhages into the skin, muscles, soft tissues and mucous membranes
✧ Prolonged bleeding post-surgery or trauma

Images courtesy by Peter A. Kouides, MD
www.bloodcmecenter.org
Life-threatening bleedings

Images courtesy by Peter A. Kouides and Guy Young
From www.bloodcmecenter.org
Replacement therapy

- Factor concentrates
  - plasma derived
  - recombinant
- Cryoprecipitate/plasma

**Desmopressin**
- mild haemophilia A

**Antifibrinolytic agents**
- adjuvants

**BUT 70%** of haemophiliacs in the world are either **not** or **poorly** treated
Haemophilia care in Europe: a survey of 19 countries

From: O’Mahony B et al. Haemophilia 2011;17:35-40
Targeted factor levels for surgical management of patients with haemophilia


<table>
<thead>
<tr>
<th>Surgery</th>
<th>FVIII</th>
<th>FIX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target level (%)</td>
<td>Duration of treatment (days)</td>
</tr>
<tr>
<td>Major surgery</td>
<td>80-100</td>
<td>60-80</td>
</tr>
<tr>
<td></td>
<td>60-80</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td>40-60</td>
<td>40-60</td>
</tr>
<tr>
<td></td>
<td>30-50</td>
<td>30-50</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>50-80</td>
<td>50-80</td>
</tr>
<tr>
<td></td>
<td>30-80</td>
<td>30-80</td>
</tr>
</tbody>
</table>

30-50% less in limited resources sites!
Subclinical deep venous thrombosis observed in 10% of hemophilic patients undergoing major orthopedic surgery

C. HERMANS,* F. HAMMER,† S. LOBET* and C. LAMBERT*

*Division of Haematology and †X-Ray Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium


- 24 haemophilia pts.
- Grade 1 stockings
- No DVT, PE

- **10% subclinical DVT**
Inhibitors represent the most serious complication
- neutralization and inactivation of residual endogenous FVIII and exogenous FVIII
- resistance to clotting factor replacement therapy

Up to 30% of patients with severe haemophilia A and 6% in haemophilia B

Bethesda assay used to confirm presence of inhibitors
An inhibitor is considered as strong when the titer is >5 BU
## Treatment choices in haemophilia patients with inhibitors

<table>
<thead>
<tr>
<th>rFVIIa</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Recombinant product</td>
<td>- Plasma-derived product containing a mixture of activated factors II, VII, IX, X</td>
</tr>
<tr>
<td>- Short half-life (2-3 hr), as measured by FVII activity</td>
<td>- Longer half-life than rFVIIa (4-7 hrs)</td>
</tr>
<tr>
<td>- Potential for thrombogenicity</td>
<td>- Potential for thrombogenicity</td>
</tr>
<tr>
<td>- Variable patient response</td>
<td>- Potential for transmission of human viruses</td>
</tr>
<tr>
<td>- 90 µg/kg every 2 hrs</td>
<td>- Anamnesis noted because of residual FVIII content</td>
</tr>
<tr>
<td></td>
<td>- Variable patient response</td>
</tr>
<tr>
<td></td>
<td>- 50-75 IU/kg every 6-8 hrs</td>
</tr>
</tbody>
</table>

**Bypassing therapy should be continued for 10-14 days postop.**

Berntorp E. Haemophilia 2009;15:3-10
Mechanisms of by-passing agent therapy

Combination therapy

Antifibrinolytic agents

Tranexamic acid (TXA) combined with recombinant factor VIII in severe hemophilia A

Increased clot stability with combination of FVIII and TXA

## Inherited deficiencies of coagulation factors (rare bleeding disorders)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Bleeding severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia</td>
<td>Usually mild, except in afibrinogenemia</td>
</tr>
<tr>
<td>II</td>
<td>Usually mild</td>
</tr>
<tr>
<td>V</td>
<td>Usually mild</td>
</tr>
<tr>
<td>Combined V + VIII</td>
<td>Usually mild</td>
</tr>
<tr>
<td>VII</td>
<td>Severe with low levels</td>
</tr>
<tr>
<td>X</td>
<td>Moderate; severe with low levels</td>
</tr>
<tr>
<td>Vitamin K dependent</td>
<td>Usually mild</td>
</tr>
<tr>
<td>XI</td>
<td>Mild- moderate with low levels</td>
</tr>
<tr>
<td>XIII</td>
<td>Severe</td>
</tr>
</tbody>
</table>
Inherited deficiencies of coagulation factors (rare bleeding disorders)

Association between level and clinical bleeding

**Strong:** FI, FII, FX, FXIII

**Poor:** FV, FVII

**No!**: FXI


Inherited deficiencies of coagulation factors (rare bleeding disorders)

Typical symptoms

- Umbilical cord, mucosal, gastrointestinal tract (GI), genitourinary or central nervous system (CNS) bleeding
- Hemarthrosis and haematomas
- Spontaneous rupture of the spleen
- Bleeding after trauma, surgery and post-partum

Thromboembolic complications!!!

FI deficiency (afibrinogenemia, dysfibrinogenemia)
FVII deficiency

Marty S et al. Haemophilia 2008;14:564-570
Mannucci PN et al. Blood 2004;104:1243-1252
### Therapeutic options for RBDs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen concentrate, Cryoprecipitate, FFP</td>
</tr>
<tr>
<td>II</td>
<td>PCC, FFP</td>
</tr>
<tr>
<td>V</td>
<td>FFP, rFVIIa, platelet transfusion</td>
</tr>
<tr>
<td>V + VIII</td>
<td>FFP, FVIII concentrate, desmopressin</td>
</tr>
<tr>
<td>VII</td>
<td>Recombinant FVIIa, FVII concentrate, PCC, FFP</td>
</tr>
<tr>
<td>X</td>
<td>FX concentrate, PCC, FFP</td>
</tr>
<tr>
<td>Vitamin K dependent</td>
<td>Vitamin K, PCC, FFP, rFVIIa</td>
</tr>
<tr>
<td>XI</td>
<td>FXI concentrate, FFP, Antifibrinolytic drugs, rFVIIa, desmopressin</td>
</tr>
<tr>
<td>XIII</td>
<td>FXIII concentrate, recombinant FXIII, Cryoprecipitate, FFP</td>
</tr>
</tbody>
</table>

Tailored to the individual situation

---

Huang JN, Koerper MA. Haemophilia 2008;14:1164-1169
### Therapeutic recommendations for RBDs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Target</th>
<th>Plasma half-life</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI</td>
<td>100-200 mg/dl</td>
<td>2-4 days</td>
<td>Every 2-4 days</td>
</tr>
<tr>
<td>FII</td>
<td>20-30 IU/dl</td>
<td>3-4 days</td>
<td>Every 2-3 days</td>
</tr>
<tr>
<td>FV</td>
<td>15 IU/dl</td>
<td>36 hours</td>
<td>Daily</td>
</tr>
<tr>
<td>FVII</td>
<td>10-15 IU/dl</td>
<td>4-6 hours</td>
<td>Every 6-8 hours</td>
</tr>
<tr>
<td>FX</td>
<td>10-20 IU/dl</td>
<td>40-60 hours</td>
<td>Daily</td>
</tr>
<tr>
<td>FXI</td>
<td>30-40 IU/dl</td>
<td>40-70 hours</td>
<td>Daily or alternate days</td>
</tr>
<tr>
<td>FXIII</td>
<td>3-10 IU/dl</td>
<td>11-14 days</td>
<td>Every 20-30 days</td>
</tr>
</tbody>
</table>

Guiding principles for surgery in patients with inherited bleeding disorders

• Only perform surgery if it is needed and is in the best interest of patient

• Do not allow elective surgery to turn into an emergency-get prepared!!

• Use the safest haemostatic product that are available
Peri-operative plan in patients with inherited bleeding disorders

Preoperative

- **Bleeding history**
  - Patient/ Family
  - Assessment of bleeding phenotype (non-bleeder, mild vs. severe bleeder)
- **Check for other bleeding risk factors**
  - Medications, co-morbidities
- **Type of surgery**
  - Risk of intraoperative & postoperative bleeding
- **Assess the risk of venous thromboembolism**
- **Check the serological status** (HIV, hepatitis and vaccination)

- Team meeting: surgeon, anesthesiologist, haematologist, nurses
- Training on factor preparation
Peri-operative plan in patients with inherited bleeding disorders

**Preoperative**

- **Check the factor level**
  - Measurement of response to therapy
  - Dose titration of therapy
- **Inhibitor screening**
  - If positive, check titre, peak, type of response
- **Check the lab capability**
  - Serial level measurements
- **Check the availability of substitution product**
  - Type, dose, regimen, sampling requirements
Summary of the peri-operative plan in patients with inherited bleeding disorders

Day of surgery

- Schedule the surgery early in the week and early in the day for optimal laboratory and blood bank support
- Check the availability of blood products
- Use oral premedication. Avoid any intramuscular injection
- Careful planning of the venous access. Reserve one iv. line for substitution therapy
Summary of the peri-operative plan in patients with inherited bleeding disorders

Day of surgery

- Reconstitute the factor product immediately prior to dosing, to avoid loss of activity and minimize the risk of bacterial contamination

- Check immediately prior to the procedure, that the factor is raised to the desired level and document the patient’s response to the replacement therapy

- Care during intubation of the airway
  Avoid naso-tracheal intubation

- Careful positioning of the extremities
Postoperatively

- Maintain daily contact with the specialized haematologist

- Check daily the factor level

- If postoperative bleeding, check the trough factor level
Postoperatively

- Prompt surgical intervention is required if bleeding continues despite adequate replacement therapy

- No injection and no invasive procedures without replacement

- Use paracetamol, selective cox-inhibitors or opioids for analgesia
- No ASA or NSAIDs

- Consider thromboprophylaxis in selected cases
Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations

**Survey**
- 15 European countries
- 26 centres
- 3633 severe haemophilia pts.
- Interventions per year per centre
  - 2-4 major interventions
  - 6-10 minor
  - > 10 dental

**Literature review**
- 35 case series
- 1114 pts.
- 1328 surgical procedures
- 707 orthopedic

**Bleeding rate: 10%**

Prospectively collected data
113 pts. with bleeding disorders
- 46% haemophilia A
- 38% VWD, 6% haemophilia B
- 5% FX deficiency
- 4% other
Age 18-86
144 procedures:
  86 surgical and 58 endoscopic
  15 urgent
  35% major
2 deaths; mortality 1.4%
4% haemorrhagic complications
10% for major operations
<table>
<thead>
<tr>
<th>Type of haemophilia</th>
<th>Type of surgery</th>
<th>Total fc VIII consumption</th>
<th>Antifibrinolytics</th>
<th>Thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild haemophilia</td>
<td>Implantation of a biological aortic valve</td>
<td>51.000 IU Advate</td>
<td>Tranexamic acid</td>
<td>Fragmin 5000IU x 1 In 6 weeks postop</td>
</tr>
<tr>
<td>Mild haemophilia</td>
<td>Ventricle resection (DOR) and mitral valve reconstruction</td>
<td>70.000 IU Advate</td>
<td></td>
<td>Aspirin 75 mg x 1</td>
</tr>
<tr>
<td>Mild haemophilia</td>
<td>CABG X 3</td>
<td>63.000 IU Kongenate</td>
<td></td>
<td></td>
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<tr>
<td>Moderate haemophilia</td>
<td>Implantation of a biological aortic valve CABG X 1</td>
<td>94.500 IU Advate</td>
<td>Tranexamic acid</td>
<td>Fragmine 7500 IU x 2 D 1-10 5000 IU x 2 D 11-M 3</td>
</tr>
<tr>
<td>Severe Haemophilia</td>
<td>CABG X 4</td>
<td>50.000 IU ReFacto</td>
<td>Tranexamic acid</td>
<td>Fragmine 7500 IU x 2 D 1-10 5000 IU x 2 D 11-M 3</td>
</tr>
<tr>
<td>Mild haemophilia</td>
<td>Aorta valve replacement CABG X 1</td>
<td>69.000 IU Advate</td>
<td>Tranexamic acid</td>
<td>Fragmine 5000 IU x 1 D1-5 5000 IU x 1 M1</td>
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</table>
ORIGINAL ARTICLE Clinical haemophilia

Applicability of the European Society of Cardiology guidelines on management of acute coronary syndromes to people with haemophilia – an assessment by the ADVANCE Working Group

P. STARITZ, P. DE MOERLOOSE, R. SCHUTGENS and G. DOLAN ON BEHALF OF THE ADVANCE WORKING GROUP
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Final tips for success

HAVE A PLAN !!!

- Accurate diagnosis and knowledge of the severity of the bleeding disorder are essential.
- Patients with inherited bleeding disorders should be managed peri-operatively in collaboration with a haematologist.
- Appropriate peri-operative replacement therapy is the mainstay of therapy.
- Thromboprophylaxis should be discussed in cases with associated risk factors.
- Good communication is key.