Key issues in advanced bleeding care
Donat R. Spahn
University Hospital of Zurich
Consulting for B. Braun, CSL Behring, Vifor International

ABC / ABC trauma faculty, managed by Thomson Physicians World GmbH (unrestricted educational grant - Novo Nordisk, CSL Behring, LFB Biomédicaments)

In the past 5 years I received honoraria / travel support for occasional consulting / lecturing:
## Honoraria / travel support for occasional consulting / lecturing

<table>
<thead>
<tr>
<th>Company</th>
<th>Company</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>AMGEN</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Baxter</td>
<td>B. Braun</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Bristol-Myers-Squibb</td>
<td>CSL Behring</td>
<td>Curacyte</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Ethicon Biosurgery</td>
<td>Fresenius</td>
</tr>
<tr>
<td>Galenica</td>
<td>GlaxoSmithKline</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>Merck Sharp &amp; Dohme</td>
<td>Novo Nordisk</td>
<td>Octapharma</td>
</tr>
<tr>
<td>Organon</td>
<td>Oxygen Biotherapeutics</td>
<td>PAION</td>
</tr>
<tr>
<td>Photonics Healthcare</td>
<td>ratiopharm</td>
<td>Roche Diagnostics</td>
</tr>
<tr>
<td>Roche Pharma</td>
<td>Schering-Plough</td>
<td>Tem International</td>
</tr>
<tr>
<td>Verum Diagnostica</td>
<td>Vifor</td>
<td></td>
</tr>
</tbody>
</table>
Bleeding in Surgery / Trauma

Surgical - Surgeon

Coagulopathy - Algorithm - Specific Treatment
Physiology of Hemostasis

- Vessel wall
- von Willebrand Factor
- Platelets
- Plasmatic Coagulation
- Fibrinolysis

Primary Hemostasis
Secondary Hemostasis
A Intact vessel wall

- Platelet
- GpIIb\(\alpha\)
- Plasma von Willebrand factor
- Nonactivated \(\alpha\)IIb\(\beta\)3
- Collagen fibrils
- Matrix von Willebrand factor
- Extracellular matrix

Endothelial cell

- Plasma vWF binds to collagen and uncoils
- Adhesion of platelets to vWF
- Tethering and rolling of platelets
- Platelets also adhere to collagen
- Platelets become activated (GPIIb/IIIa) and undergo a shape change
C Platelet-plug formation

- Release of thromboxane A2, ADP and vWF to recruit and activate additional platelets
- Activation (inside-out) of the GPIIb/IIIa receptors enabling the inter-platelet connection with fibrinogen (         ) \( \Rightarrow \) platelet aggregation
- Activated platelets provide a highly efficient surface for activated coagulation factors enabling the thrombin burst (cell based model)
Fibrinogen

Fibrin soluble monomer

F XII

F XIII

F XIIIa

Fibrin insoluble fibrin strand

Hemostasis in massive bleeding

- Fibrinogen is in a central position of the coagulation system
  - Platelet aggregation
  - Plasmatic coagulation

- Fibrinogen is the coagulation „element“ that becomes critically reduced first in many clinical situations

- The critical level may be < 1.5 – 2.0 g/L or a MCF in FIBTEM of < 7 mm (< 10 mm ?)

- No fibrinogen stores in the body that might be mobilized

Spahn D. R. et al. Critical Care (2013) 17:R76
TEG ® / ROTEM®
Diagnostics: Viscoelastic Techniques

TEG®

ROTEM®

Management of bleeding following major trauma: an updated European guideline

Rolf Rossaint¹, Bertil Bouillon², Vladimir Cerny³, Timothy J Coats⁴, Jacques Duranteau⁵, Enrique Fernández-Mondéjar⁶, Beverley J Hunt⁷, Radko Komadina⁸, Edmund Neugebauer¹⁰, Yves Ozier¹¹, Louis Riddez¹², Arthur Schultz¹³, Jean-Louis Vincent¹⁴, and Donat R Spahn¹⁵

Rossaint R. et al., Critical Care (2010) 14:R52
Spahn D. R. et al. Critical Care (2013) 17:R76
## Emergency Coagulation Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Vit K Antagonist</th>
<th>Anti Xa</th>
<th>Anti IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT</strong></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti Xa (LMWH)</strong></td>
<td></td>
<td>↑↑↑</td>
<td></td>
</tr>
<tr>
<td><strong>TT</strong></td>
<td></td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

- **Laboratory tests**
  - Fibrinogen concentration
  - NOAC plasma concentrations
  - Platelet number

- **TEG ® / ROTEM®**

- **Treatment immediately after lab / ROTEM ® tests**
  - Tranexamic acid (1 gr iv) if not received en route
  - Fibrinogen (2-4 gr iv in very severe cases)
We recommend that routine practice to detect post-traumatic coagulopathy include the measurement of international normalised ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelets. INR and APTT alone should not be used to guide haemostatic therapy.

Grade 1C
We recommend that thrombelastometry also be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy.
We recommend early treatment with thawed FFP in patients with massive bleeding.

Grade 1B, old

We recommend the initial administration of plasma [fresh frozen plasma (FFP) or pathogen-inactivated plasma] (Grade 1B) or fibrinogen (Grade 1C) in patients with massive bleeding.

Grade 1B/C, new

Spahn D. R. et al. Critical Care (2013) 17:R76
If further plasma is administered, we suggest an optimal plasma:red blood cell ratio of at least 1:2.

Grade 2C, new

We recommend that plasma transfusion be avoided in patients without substantial bleeding.

Grade 1B, new

Spahn D. R. et al. Critical Care (2013) 17:R76
Original Investigation

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma
The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin F. Fox, PhD; Charles F. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy L. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O’Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jennie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David R. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

PRT in 680 severely injured patients performed in 12 level I trauma centers in the US (initially planned were 580 patients, DSMB increased #)

Blood product ratios: 1:1:1 vs. 1:1:2

Primary outcome: 24h and 30d all cause mortality

Secondary outcomes:
- Time to hemostasis
- Blood product volumes transfused
- Complications
- Incidence of surgical procedures
- Functional status

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma

The PROPPR Randomized Clinical Trial

1:1:1 - identical packs of 6
1 u platelets (6-pack) to be given first
6 u thawed plasma
6 u RBC

Blood product ratios: 1:1:1 vs. 1:1:2
Platelet:Plasma:RBC

Primary outcome: 24h and 30d all cause mortality

Secondary outcomes:
- Time to hemostasis
- Blood product volumes
- Complications
- Incidence of surgical procedures
- Functional status

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma: The PROPPR Randomized Clinical Trial

1:1:1 - identical packs of 6
1 u platelets (6-pack) to be given first
6 u thawed plasma
6 u RBC

Blood product ratios: 1:1:1 vs. 1:1:2

Primary outcome: 24h

Secondary outcomes:
- Time to hemostasis
- Anatomic hemostasis in the operating room was defined as an objective assessment by the surgeon including within the surgical field was controlled and no further hemostatic interventions were anticipated. In the intervention group, a 1:1:2 ratio of blood products was used. This ratio was different from the control group, which received a 1:1:1 ratio. The study was conducted in 12 level I trauma centers in the US (initially planned were 580 patients, DSMB increased #)

1:1:2 – 2 different packs of 6
First and all odd-numbered packs
0 u platelets (6-pack)
3 u thawed plasma

Secondary outcomes:
- Time to hemostasis
- Blood product volumes transfused
- Complications
- Incidence of surgical procedures

Blinding?

Table 2. Trial Outcomes by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1:1:1 Group (n = 338)</th>
<th>1:1:2 Group (n = 342)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h Mortality, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>43 (12.7)</td>
<td>58 (17.0)</td>
<td>.12</td>
</tr>
<tr>
<td>30-d Mortality, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75 (22.4)</td>
<td>89 (26.1)</td>
<td>.26</td>
</tr>
<tr>
<td>Achieved hemostasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>291 (86.1)</td>
<td>267 (78.1)</td>
<td>.006</td>
</tr>
<tr>
<td>Analomic, median (IQR), min&lt;sup&gt;c&lt;/sup&gt;</td>
<td>105 (64 to 179)</td>
<td>100 (56 to 181)</td>
<td>.44</td>
</tr>
<tr>
<td>Hospital-free days, median (IQR)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>1 (0 to 17)</td>
<td>0 (0 to 16)</td>
<td>.83</td>
</tr>
<tr>
<td>Ventilator-free days&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 (0 to 16)</td>
<td>7 (0 to 14)</td>
<td>.14</td>
</tr>
<tr>
<td>ICU-free days&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (0 to 11)</td>
<td>4 (0 to 10)</td>
<td>.10</td>
</tr>
<tr>
<td>Incidence of primary surgical procedure</td>
<td>290 (85.8)</td>
<td>284 (83.0)</td>
<td></td>
</tr>
<tr>
<td>Disposition at 30 d, No. (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>118 (34.9)</td>
<td>105 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Remained hospitalized</td>
<td>82 (24.3)</td>
<td>77 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Other&lt;sup&gt;f&lt;/sup&gt;</td>
<td>59 (17.5)</td>
<td>71 (20.8)</td>
<td>.37</td>
</tr>
<tr>
<td>Mortal&lt;sup&gt;g&lt;/sup&gt;</td>
<td>75 (22.2)</td>
<td>89 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome Scale-Extended score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4 (3 to 6)</td>
<td>4.5 (3.5 to 7.0)</td>
<td>.11</td>
</tr>
</tbody>
</table>
Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage

- Observational study in severely injured patients performed in 3 major trauma centers (n=106)
- Protocols: 1:1:1 to protocols with additional cryo
- Coagulation assessed after 4, 8, 12 RBCs using ROTEM and standard lab values
1:1:1 Magic for the uneducated?

PRT (n = 78)
28 day mortality in ITT population
32% (1:1:1) vs. 14% (control)
RR 2.27 (CI 0.98 – 9.63)

Log-rank $p = 0.053$

Nascimento B. et al. CMAJ (2013) 185: E583
We recommend that platelets be administered to maintain a platelet count above $50 \times 10^9/l$.

Grade 1C

Spahn D. R. et al. Critical Care (2013) 17:R76
We suggest maintenance of a platelet count above $100 \times 10^9/l$ in patients with multiple trauma who are severely bleeding or have TBI.

Grade 2C

We suggest an initial dose of four to eight platelet concentrates or one aphaeresis pack.

Grade 2C

Spahn D. R. et al. Critical Care (2013) 17:R76
R-26 Fibrinogen

We recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by thrombelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 to 2.0 g/l.

Grade 1C

Spahn D. R. et al. Critical Care (2013) 17:R76
Fibrinogen concentration

No coagulation therapy
Fibrinogen only
Fibrinogen + PCC

R-29 Prothrombin complex concentrate (PCC)

We recommend the use of prothrombin complex concentrate for the emergency reversal of vitamin K-dependent oral anticoagulants.

Grade 1B

Spahn D. R. et al. Critical Care (2013) 17:R76
If a concentrate-based goal-directed strategy is applied, we suggest that PCC be administered in the bleeding patient with thrombelastographic evidence of delayed coagulation initiation.

Grade 2C
Success of TEG ® / ROTEM® and factor concentrate based algorithms in trauma
Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM®)-guided administration of fibrinogen concentrate and prothrombin complex concentrate


Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy

Herbert Schöchl1, Ulrike Nienaber2, Marc Maegel3, Gerald Hochleitner2, Florian Primavesi2, Beatrice Steitl4, Christian Arnul5, Alexander Farkas6, Wolfgang Voelckel7, and Cristina Solomon8

- Mortality ↓ < expected mortality (TRISS, RISC)
- Need for transfusion ↓
- LOS ↓

Algorithm for treating bleeding in patients with trauma-induced coagulopathy

Temperature
NRA
Electrolytes
Blood cell count

Optimize preconditions

Temperature >34°C
pH >7.2
Calcium >1 mmol/L
Haematocrit >24%

TXA 15–20 mg/kg BW

Run ROTEM (EXTEM, INTEM, FIBTEM, APTEM)*

1. Focus on: hyperfibrinolysis
EXTEM CT > APTEM CT

Treat fibrinolysis
TXA 15–20 mg/kg BW

Increase FIBTEM CA10 to 10–12 mm

Fibrinogen concentrate 2–6 g
(Cryoprecipitate, FFP)

2. Focus on: fibrin deficit
FIBTEM CA10 < 7 mm

Increase coagulation factor deficiency
PCC 20 U/kg BW

Thrombin generation deficit
EXTEM CT > 80 sec
(with EXTEM CT = APTEM CT)

Treat immediately

Severe clot deficiency
EXTEM CA10 < 30 mm

TXA 15–20 mg/kg BW

Increase platelet count

Platelet concentrate

3. Focus on: thrombin generation deficit
EXTEM CT > 80 sec
(with EXTEM CT = APTEM CT)

Fibrinogen concentrate 6–8 g and
PCC 20–30 U/kg BW
(Cryoprecipitate, FFP [high doses])

Platelet concentrate (increase platelet count
to ≥ 250,000/μL)

4. Focus on: platelet deficit
EXTEM CA10 < 40 mm
(with FIBTEM CA10 > 12 mm
and platelet count ≥ 50,000/μL)

Later on, repeat step 2 if necessary

Platelet concentrate

5. Focus on: severe shock
ISS > 16

Platelet concentrate

Platelet concentrate

Platelet concentrate

Platelet concentrate
Algorithm for Treating Bleeding Patients with Trauma-induced Coagulopathy

- Temperature
- BGA
- Electrolytes
- Hematocrit

Optimize preconditions

Temperature > 34°C
pH > 7.2
Calcium > 1 mmol/L
Hematocrit > 24%

Severe trauma (ISS > 16) and/or severe shock

Treat (hyper)fibrinolysis

TXA: 15-20 mg/kg BW

Run ROTEM® (EXTEM, INTEM, FIBTEM, APTEM)*

1. **Focus on: fibrin deficit**
   - FIBTEM CA<sub>10</sub> < 7mm
   - Reassess after treatment
   - Increase FIBTEM CA<sub>10</sub> to 10-12mm
     - FC: FIBTEM CA<sub>10</sub> 0-3mm: 6g
       - FIBTEM CA<sub>10</sub> 4-6mm: 3-4g

2. **Focus on: thrombin generation deficit**
   - EXTEM CT > 80 sec
   - Reassess after treatment
   - Treat coagulation factor deficiency
     - PCC: CT 81-100 s: 500-6000U
       - CT 101-120 s: 1000-1200U
       - CT > 120 s: 1500-1800U
       - and/or
       - FFP: 15-30 mL/kg BW

3. **Focus on: platelet deficit**
   - EXTEM CA<sub>10</sub> < 40mm (while FIBTEM CA<sub>10</sub> > 12mm and platelet count < 50,000/µL)
   - Reassess after treatment
   - Increase EXTEM CA<sub>10</sub>
     - Platelet concentrate

**Severe clot deficiency**

- EXTEM CA<sub>10</sub> < 30mm
- Reassess after treatment

- TXA: 15-20 mg/kg BW
- FC: 6-8g
- PCC: 20-30 U/kg BW
  - or FFP: 30 mL/kg BW
- Platelet concentrate: 2 U
Compliance with Recommended Care at Trauma Centers: Association with Patient Outcomes

Shahid Shafi, MD, MPH, FACS, Sunni A Barnes, PhD, Nadine Rayan, MHA, Rustam Kudyakov, MD, Michael Foreman, MD, FACS, H Gil Cryer, MD, PhD, FACS, Hasan B Alam, MD, FACS, William Hoff, MD, FACS, John Holcomb, MD, FACS

- Retrospective study in 5 Level I US trauma centers with 3,867 patients
- Primary outcome
  - Compliance with trauma treatment guidelines (22 common items / processes)
  - Association between compliance with trauma treatment guidelines (22 common items / processes) and outcome

Patients who received all recommended care were 58% less likely to die (OR 0.42; 95% CI 0.28-0.62) compared with those who did not. Observed-to-expected (TRISS) mortality was 0.89 in the suboptimal treatment group vs. 0.49 in the optimal treatment group.

Comparison between 2011 (1:1:1) vs. 2013 (early goal directed) coagulation management

Patients with ISS > 15 and 3 RBC transfused

Primary outcome: RBC, FFP and platelet transfusions

Secondary outcomes:

→ Time to hemostasis

Patients with ISS >15 and ≥3 U of PRBC:

<table>
<thead>
<tr>
<th>Blood components transfused within 24 hr</th>
<th>2011</th>
<th>2013</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC (U)</td>
<td>Mean (SD)</td>
<td>8.09 (6.7)</td>
<td>6.5 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>5 (6.0)</td>
<td>4 (5.5)</td>
</tr>
<tr>
<td>PTL (U)</td>
<td>Mean (SD)</td>
<td>4.18 (5.9)</td>
<td>2.68 (4.75)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>0 (6)</td>
<td>0 (6)</td>
</tr>
<tr>
<td>Plasma (U)</td>
<td>Mean (SD)</td>
<td>8.97 (9.47)</td>
<td>4.21 (4.61)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Outcome:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2011</th>
<th>2013</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead within 24 hr</td>
<td>8 (6.15%)</td>
<td>3 (3.12%)</td>
<td>0.361</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>26 (20.0%)</td>
<td>13 (13.5%)</td>
<td>0.218</td>
</tr>
</tbody>
</table>
Table 5 Estimated cost for blood, blood components, factors and point-of-care tests over the two periods (2011 versus 2013)

<table>
<thead>
<tr>
<th></th>
<th>Estimated cost for 1 U</th>
<th>2011</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Units (N)</td>
<td>Overall</td>
<td>Units (N)</td>
</tr>
<tr>
<td>PRBC</td>
<td>€186</td>
<td>1,048 €194,928</td>
<td>625</td>
</tr>
<tr>
<td>Plasma</td>
<td>€60</td>
<td>1,167 €70,020</td>
<td>405</td>
</tr>
<tr>
<td>PTL</td>
<td>€115</td>
<td>538 €61,870</td>
<td>258</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>€326,818</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>€400 (1 g)</td>
<td>0 0</td>
<td>134 g €53,600</td>
</tr>
<tr>
<td>POC tests</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*POC, Point of care; PRBC, Packed red blood cells; PTL, Platelets.

Savings: 76’335 Euro

## ISS and mortality: Europe vs. US

<table>
<thead>
<tr>
<th>Paper</th>
<th>ISS</th>
<th>Hospital Mortality Individualized Treatment Group with Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holcomb 2013</td>
<td>26 (17 – 36)</td>
<td>25%</td>
</tr>
<tr>
<td>Holcomb 2015</td>
<td>26.5 (17 – 41)</td>
<td>24%</td>
</tr>
<tr>
<td>Nascimento 2013</td>
<td>35 ± 13</td>
<td>14%</td>
</tr>
<tr>
<td>Schöchl 2011</td>
<td>35.2</td>
<td>7.5%</td>
</tr>
<tr>
<td>Innerhofer 2013</td>
<td>37 (29 – 50)</td>
<td>8%</td>
</tr>
<tr>
<td>Waifsade 2013</td>
<td>37.1 – 37.6</td>
<td>26% (no algorithm)</td>
</tr>
<tr>
<td>Nardi 2015</td>
<td>33 (15 – 51)</td>
<td>14%</td>
</tr>
</tbody>
</table>

Nascimento B. et al. CMAJ (2013) 185: E583
Innerhofer P. et al., Injury (2013) 44: 209
Wafaisade A. et al., J Trauma Acute Care Surg (2013) 74: 387
Nardi G. et al., Crit Care (2015) 18: 83
Conclusion

- Coagulopathy is frequent after major trauma
- Fibrinogen is the coagulation „element“ that becomes critically reduced first in many trauma patients
- Immediate and repeated viscoelastic coagulation monitoring is key for individualized goal-directed coagulation algorithms
- Having a individualized goal-directed coagulation algorithm in is mandatory in every hospital
- Implementation is key for its success

Spahn D. R. et al. Critical Care (2013) 17:R76
Idarucizumab for Dabigatran Reversal

- 90 patients on long term dabigatran with serious bleeding or requiring urgent procedure
- Idarucizumab 5 gr iv-infusion (5 min)

**Outcome**

- Reversal of dTT, TT, aPTT, ECT (ecarin clotting time)


This article was published on June 22, 2015, at NEJM.org.
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

- 74 volunteers treated with 2 x 5 mg apixaban or 1 x 20 mg rivaroxaban daily
- Andexanet 400 / 800 mg + 2h infusion (2h)

Outcome

- Anti-Xa activity
- Free apixaban / rivaroxaban concentration
- Thrombin generation

Pig study (n=24): Liver injury
High dose dabigatran (1'160 ng/ml)
3 doses of idarucizumab
Mortality: 6/6 vs. 1/18

Applying ‘Patient Blood Management’ in the trauma center

Oliver M. Theusinger, Philipp Stein, and Donat R. Spahn
<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative history</td>
<td>ROTEM® after anesthesia induction</td>
</tr>
<tr>
<td>1. Drugs affecting coagulation</td>
<td>- Transplant surgery</td>
</tr>
<tr>
<td>- Antiplatelet drugs</td>
<td>- Cardiac and vascular surgery</td>
</tr>
<tr>
<td>- Heparin</td>
<td>- Difficult cancer surgery</td>
</tr>
<tr>
<td>- Oral anticoagulation (Vit. K antagonists, Xa antagonists, IIa antagonists)</td>
<td>- Liver insufficiency</td>
</tr>
<tr>
<td>2. Coagulation status?</td>
<td>- Intra-abdominal sepsis</td>
</tr>
<tr>
<td>3. HIT II?</td>
<td>- Emergency room entry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood loss &gt; 50% with diffuse bleeding</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ROTEM® analysis</th>
<th>Target values</th>
</tr>
</thead>
<tbody>
<tr>
<td>- EXTEM, INTEN, FIBTEM, APTEM</td>
<td>- Normothermia (Temp. &gt; 35°C)</td>
</tr>
<tr>
<td>- HEPTEM in heart and vascular surgery</td>
<td>- Normocalcaemia (Ca &gt;1.15 mmol/l)</td>
</tr>
<tr>
<td></td>
<td>- No acidosis (pH &gt; 7.2)</td>
</tr>
<tr>
<td></td>
<td>- Hematocrit &gt; 0.21</td>
</tr>
<tr>
<td></td>
<td>- Hypotension (MAP 55-60 mmHg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Crystalloid and/or colloid volume substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIBTEM &lt; 7 mm</td>
</tr>
<tr>
<td>INTEM (CT and CFT prolonged) and HEPTEM normal or ACT pathological and heparinase ACT normal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>EXTEM / INTEN: Decrease of MCF after maximum was reached</td>
</tr>
<tr>
<td>APTEN: normal</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>On-going diffuse bleeding</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXTEM / INTEM MCF&lt;40 mm</strong></td>
<td>Fibrinogen up to 6 g, followed by <em>Factor XIII</em> 15 U/kg BW crystalloid and colloid volume substitution</td>
</tr>
<tr>
<td>CT EXTEM / INTEM normal</td>
<td></td>
</tr>
<tr>
<td>MCF FIBTEM &lt; 7mm</td>
<td>Platelet concentrates</td>
</tr>
<tr>
<td>Hct &gt; 0.21</td>
<td></td>
</tr>
<tr>
<td>MCF FIBTEM &gt; 7mm</td>
<td>Target of <em>Factor XIII</em>: &gt; 60% (<em>Factor XIII</em> 15 U/kg BW)</td>
</tr>
<tr>
<td>Platelets &lt; 50 000/μl (&lt; 100 000/μl in cardiac surgery or in patients suffering from traumatic brain injury)</td>
<td>Target of <em>Factor V</em>: &gt; 20% (in particular in liver insufficiency / trauma or intra-abdominal sepsis: 2-4 U FFP)</td>
</tr>
<tr>
<td>Coagulation test incl. F XIII, F V, INR, PT, aPTT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>On-going diffuse bleeding</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quick’s value &lt; 30% and</td>
<td></td>
</tr>
<tr>
<td>Factor V &gt; 20%</td>
<td>4 <em>factor prothrombin complex concentrate</em> 1000-2000 IU</td>
</tr>
<tr>
<td>OR</td>
<td>- Factor II, VII, IX and X</td>
</tr>
<tr>
<td>EXTEM / INTEM: CT, CFT prolonged</td>
<td>Depending on the patients’ bodyweight</td>
</tr>
<tr>
<td><strong>In case of massive transfusion</strong></td>
<td>Target Hematocrit: 0.21 – 0.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>If massive diffuse bleeding continues and</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated acidosis</strong></td>
<td>Recombinant Factor VIIa</td>
</tr>
<tr>
<td>Treated hypothermia</td>
<td>60 μg/kg/Body weight i.v.</td>
</tr>
<tr>
<td>Excluded Hypocalcaemia</td>
<td>A second dose of 60 μg/kg/Bodyweight i.v. can be given again</td>
</tr>
<tr>
<td>Hematocrit: 0.21 – 0.24</td>
<td>after 2-4 hours, if bleeding has not completely stopped.</td>
</tr>
<tr>
<td>Excluded DIC</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen was substituted</td>
<td></td>
</tr>
<tr>
<td>Platelets &gt; 50 000/μl (&gt; 100 000/μl in cardiac surgery or in patients suffering from traumatic brain injury)</td>
<td></td>
</tr>
</tbody>
</table>