Platelet transfusion for perioperative management of patients on antiplatelet therapy

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Financial disclosures

• Bayer Healthcare
• Bristol-Myers Squibb
• Novartis
• Macopharma
• ASPEN
• Boehringer Ingelheim

• Transfusion Medicine in Greifswald produces and markets platelet concentrates
• MACCE
  major adverse cardiac and cerebrovascular events

• Patients with low to moderate MACCE risk

• Patients with high MACCE risk

• Desmopression, tranexamic acid

• Platelet transfusion

• Antidots for anti-platelet drugs
Antiplatelet Drugs

Cyclooxygenase Inhibitors
• Aspirin

P2Y_{12} (ADP)-Receptor Inhibitors
• Clopidogrel
• Prasugrel
• Ticagrelor (reversibel)

Protease-activated receptor-1 Inhibitors
• Vorapaxar (triple therapy)
## Risk Stratification of Patients

**MACCE-Risk: major adverse cardiac and cerebrovascular events**

<table>
<thead>
<tr>
<th>History</th>
<th>High risk &gt;10%/year</th>
<th>Moderate risk 5-10%/year</th>
<th>Low risk &lt;5%/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug eluting stent</td>
<td>&lt; 6 - 12 months</td>
<td>&gt; 6 - 12 ; &lt;24 months</td>
<td>&gt; 24 months</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>&lt; 3 months</td>
<td>&gt; 3 ; &lt;12 months</td>
<td>&gt; 12 months</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>&lt; 3 months</td>
<td>&gt; 3 months</td>
<td>-</td>
</tr>
<tr>
<td>CHADS$_2$-score</td>
<td>5-6</td>
<td>2-4</td>
<td>0-1</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>-</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Platelet inhibition</td>
<td>dual</td>
<td>mono/dual</td>
<td>mono</td>
</tr>
</tbody>
</table>

Spyropoulos et al. JTH 2013
Management of Low to Moderate Risk Patients on Aspirin: POISE-ll-study

MI/death: 7.0% on aspirin; 7.1% off aspirin, p=0.92

Bleeds: 4.6% on aspirin; 3.8% off aspirin, p<0.05

Devereaux et al. NEJM 2014
Main Results of POISE II Study

• Perioperative aspirin does not prevent myocardial infarction

• Perioperative aspirin increases the bleeding risk

• Stop aspirin 3 days before surgery

• Restart aspirin 7 days after surgery
How to manage patients on antiplatelet drugs

• who require urgent surgery (within 12-24 hours) with high bleeding risk

• with high MACCE risk (recent stents, recent ACS)

Coronary artery 3 months after Sirolimus-Stent implantation

Hao et al. Circ J. 2011
Potential Approaches

Indirect approaches (do not target antiplatelet drugs):

• Platelet transfusion
  • Desmopressin (DDAVP)
  • Tranexamic acid
  • rFVIIa (Novoseven)

Direct approach (target antiplatelet drugs):

• specific antidotes
Desmopressin for cardiac surgery in patients under APT

Resurgery because of bleeding, n=413

Peto Odds Ratio
Peto, Fixed, 95% CI

No difference in thrombotic complications

POR: 0.39; 95% CI: 0.18–0.84

Desborough et al. JTH 2017
Tranexamic acid in cardiac surgery

n=4662, ~17% with ASA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tranexamic acid</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke, thrombosis</td>
<td>16.7%</td>
<td>18.1%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Resurgery due to bleeding</td>
<td>0.8%</td>
<td>2.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBC-Transfusion</td>
<td>32.8%</td>
<td>46.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Halbierung der Dosis nach 1392 Patienten

adapted from Myles et al. NEJM 2017
Potential Approaches

Indirect approaches (do not target antiplatelet drugs):

• Platelet transfusion
• Desmopressin (DDAVP)
• Tranexamic acid
• rFVIIa (Novoseven)

Direct approach (target antiplatelet drugs):

• specific antidotes
Platelet transfusion reverses triple APT: aspirin, clopidogrel, voraxapar

Macaques, n≥6

Human platelets

Human plasma

Reversal of aspirin and clopidogrel

Light transmission aggregometry mixing study: fresh platelets added to inhibited platelets

Li et al.; JTH 2012
Less platelets to reverse aspirin?

- Transfused platelet: Thromboxane–Synthesis and release
- Circulating platelet: Thromboxane synthesis blocked by aspirin
  - active $\text{TXA}_2$-receptor
  - Platelet activation
Active metabolites inhibit fresh platelets

Light transmission aggregometry mixing study:
fresh platelets added to inhibited platelets

[Graph showing the effect of different concentrations of prasugrel's active metabolite on platelet aggregation over time. The x-axis represents post-dose time points (h), and the y-axis represents mean MPA. The graph includes lines for 80%, 60%, 40%, and 0% concentrations, with the 80% line showing the greatest decrease in platelet aggregation.]
<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of action</th>
<th>Time to peak level</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Irreversible inhibition of COX-1 and COX-2</td>
<td>30-40 min*</td>
<td>15-30 min</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Irreversible inhibition of P2Y$_{12}$ ADP receptor</td>
<td>1 h for circulating drug</td>
<td>Active metabolites circulate for up to 8 h</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Irreversible inhibition of P2Y$_{12}$ ADP receptor</td>
<td>30 min</td>
<td>7 h</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Reversible inhibition of P2Y$_{12}$ ADP receptor</td>
<td>1.5 h</td>
<td>7 h</td>
</tr>
<tr>
<td>Voraxapar</td>
<td>Reversible* inhibition of PAR-1 receptor</td>
<td>1-2 h</td>
<td>126–269 h</td>
</tr>
</tbody>
</table>

*slow dissociation – functionally irreversible
Adapted from Ortel Blood 2012, French et al. Blood Reviews 2014, Voraxapar prescribing info
Inability of fresh platelets to reverse Ticagrelor

Light transmission aggregometry mixing study: fresh platelets added to inhibited platelets


Godier et al. NEJM 2015
- Transfused platelets will be inhibited for at least 48-72h, despite the short half life of 7-8h

**Very good in-vitro study**
Bertling A. et al JTH 2018 in press
Platelet function testing to estimate the bleeding risk

<table>
<thead>
<tr>
<th>Test</th>
<th>ROC AUC</th>
<th>Cut-off (U)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>0.73</td>
<td>22</td>
<td>63</td>
<td>85</td>
<td>75</td>
<td>76</td>
</tr>
</tbody>
</table>

Malm et al., BJA 2016
Platelet function testing

• Which test to use?
  • Multiplate
  • PFA100
  • LTA
  • WASP-Assay
  • Verify now

• What to do with discrepant results?
• 24/7 availability??
Platelet Transfusion As Rescue Strategy

• transiently improving hemostasis during surgery
  prevention of bleeding

• Rapid inhibition of transfused platelets 6h after surgery:
  prevention of in-stent thrombosis
Coronary Occlusion

-24h

Bleeding

-2h

RISK

STOP

aspirin 100mg
clopidogrel 75mg

+ 6h

2 platelet concentrates

+ 12h - 48 h

aspirin 100mg
clopidogrel 75mg

surgery

Thiele et al. JTH 2012
## Pilot study (n=14)

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Type of surgery</th>
<th>Indication for aspirin + clopidogrel</th>
<th>Time between event and surgery</th>
<th>Bleeding complications</th>
<th>Coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>11 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>76</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>5 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>54</td>
<td>Neurosurgery</td>
<td>DES (renal artery stent)</td>
<td>9 days</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>65</td>
<td>Neurosurgery</td>
<td>STEMI</td>
<td>11 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>80</td>
<td>Neurosurgery</td>
<td>BMS</td>
<td>4 weeks</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>72</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>3 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>61</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>5 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>71</td>
<td>Orthopedic surgery</td>
<td>coronary stenosis</td>
<td>n.d.</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>84</td>
<td>Orthopedic surgery</td>
<td>transcathedral aortic valve</td>
<td>3 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>82</td>
<td>Orthopedic surgery</td>
<td>DES</td>
<td>6 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>63</td>
<td>Orthopedic surgery</td>
<td>DES</td>
<td>6 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>76</td>
<td>Trauma</td>
<td>DES</td>
<td>2 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>70</td>
<td>Urology</td>
<td>DES</td>
<td>4 months</td>
<td>prolonged bleeding</td>
<td>no</td>
</tr>
<tr>
<td>69</td>
<td>Abdominal surgery</td>
<td>DES</td>
<td>4 months</td>
<td>no</td>
<td>NSTEMI</td>
</tr>
</tbody>
</table>

Thiele et al. JTH 2012
Do platelet transfusions increase the risk for arterial thrombosis?
## Patient characteristics (n=181)

Median age: 75 (42-99)

<table>
<thead>
<tr>
<th>MACCE-risk</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>63</td>
<td>34.8</td>
</tr>
<tr>
<td>moderate</td>
<td>103</td>
<td>56.9</td>
</tr>
<tr>
<td>low</td>
<td>15</td>
<td>8.3</td>
</tr>
<tr>
<td>coronary drug eluting</td>
<td>38</td>
<td>21.0</td>
</tr>
<tr>
<td>coronary bare metal</td>
<td>40</td>
<td>22.1</td>
</tr>
<tr>
<td>coronary unknown</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>cerebral vessels</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>peripheral bare metal</td>
<td>4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stents</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>coronary bypass</td>
<td>25</td>
<td>13.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bypass</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>coronary bypass</td>
<td>25</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Baschin et al. JTH 2018 in press
## Antiplatelet therapy (n=181)

<table>
<thead>
<tr>
<th>drug</th>
<th>dual</th>
<th>P2Y$_{12}$-inhibitor</th>
<th>aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>72</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>64</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>prasugrel</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ticagrelor</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baschin et al. JTH 2018 in press
Surgical procedures

Neurosurgery: 69
General Surgery: 64
Orthopedic: 25
Urology: 14
Otolaryngology: 6
Gynecology: 3

Baschin et al. JTH 2018 in press
Restart of antiplatelet therapy after surgery

Baschin et al. JTH 2018 in press
# Cardiac adverse events (n=10)

<table>
<thead>
<tr>
<th>Event</th>
<th>onset after surgery [days]</th>
<th>lethal</th>
<th>intervention</th>
<th>MACCE - risk</th>
<th>cardiac stents</th>
<th>APT when event occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTEMI</td>
<td>2</td>
<td>no</td>
<td>General surgery</td>
<td>high</td>
<td>DES</td>
<td>ASA</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>29</td>
<td>no</td>
<td>General surgery</td>
<td>high</td>
<td>DES</td>
<td>ASA</td>
</tr>
<tr>
<td>STEMI</td>
<td>1</td>
<td>no</td>
<td>General surgery</td>
<td>high</td>
<td>DES</td>
<td>ASA</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1</td>
<td>yes</td>
<td>General surgery</td>
<td>moderate</td>
<td>BMS</td>
<td>no</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>10</td>
<td>no</td>
<td>Orthopaedic</td>
<td>high</td>
<td>none</td>
<td>ASA</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>14</td>
<td>no</td>
<td>Orthopaedic</td>
<td>high</td>
<td>none</td>
<td>ASA</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>9</td>
<td>yes</td>
<td>Neurosurgery</td>
<td>moderate</td>
<td>none</td>
<td>ASA</td>
</tr>
<tr>
<td>Troponin</td>
<td>2 hours</td>
<td>no</td>
<td>General surgery</td>
<td>moderate</td>
<td>none</td>
<td>ASA</td>
</tr>
<tr>
<td>Troponin</td>
<td>23</td>
<td>no</td>
<td>Neurosurgery</td>
<td>high</td>
<td>none</td>
<td>ASA</td>
</tr>
<tr>
<td>Troponin</td>
<td>1</td>
<td>no</td>
<td>General surgery</td>
<td>high</td>
<td>DES</td>
<td>ASA</td>
</tr>
</tbody>
</table>

**no coronary thrombosis**
Bleeding in the area of surgery (n=22; 12.2%)

- Aspirin: 8.0% total, 4.5% major bleeds (Poise-II criteria)
- Dual: 12.7% total, 7.0% major bleeds (Poise-II criteria)
- Clopidogrel: 23.8% total, 19% major bleeds (Poise-II criteria)

Days after surgery: 0 5 10 15 20 25 30

% of patients without bleeding

Baschin et al. JTH 2018 in press
Conclusion

• Platelet transfusions allow urgent surgery in patients on antiplatelet therapy at high risk for arterial thrombosis and bleeding.
• Platelet transfusions are not associated with a high risk for coronary thrombosis (0/181 patients).
• This population has a high bleeding risk for the first 10 days after surgery.

These data provide the basis for a prospective trial on platelet transfusion to manage (urgent) surgery in high risk patients on antiplatelet therapy.
Potential Approaches

Indirect approaches (do not target antiplatelet drugs):
- Platelet transfusion
- Desmopressin (DDAVP)
- Tranexamic acid
- rFVIIa (Novoseven)

Direct approach (target antiplatelet drugs):
- specific antidotes
Antidote for Ticagrelor

Fab-Fragment binding Ticagrelor and its active metabolite

Buchanan et al. Blood 2015
Removal of Ticagrelor using Cytosorb-Filters

Human Blood Experiments

Whole Blood + Ticagrelor

Infusion Pump

CytoSorb

99% Ticagrelor Removal

Percent removal rate of Ticagrelor from whole blood

Time of blood sampling

3 hours

7 hours

Angheloiu JACC:BTTS 2017
Bridging with Cangrelor or GPIIb/IIIa Antagonist

- Hospitalize patients presurgery for i.v infusion for 5 days?
- Not feasible for urgent surgery

- 5-7 days pre-surgery
- 6-12h presurgery
- Surgery
- Restart of APT
For Clinical Praxis: Greifswald Approach

• Low to intermediate MACCE risk: POISE2

• stop APT 5 days before surgery,
• restart 6-7 days post surgery
For Clinical Praxis: Greifswald Approach

High risk patients, elective surgery:

day -7: replace ticagrelor by clopidogrel maintain ASA
day -1: last intake of APT
day of surgery: NO APT!!

high bleeding risk: 2 PCs 1-2 h before surgery.
moderate bleeding risk: 2 PC in case of bleeding.
restart ASA 6-8h after end of surgery; P_{2Y_{12}} 48-96h later depending on postoperative situation
For Clinical Praxis: Greifswald Approach

- Emergency surgery: wait until 6-8 h after last APT intake. Then same procedure as described above

- Unresolved: emergency surgery in ticagrelor patients
Randomized Trial
Platelet Transfusion vs ???????

Greifswald
We have an open position for a physician researcher
Bridging with GPIIb/IIIa Antagonist in Stent-Patients: Metaanalysis: 280 patients (125 cardiac, 155 non-cardiac surgery)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td>1.3%</td>
<td>0.3–3.0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7.4%</td>
<td>2.8–14.1</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>20.6%</td>
<td>4.8–43.2</td>
</tr>
<tr>
<td>Death</td>
<td>3.5%</td>
<td>1.7–5.9</td>
</tr>
<tr>
<td>MI</td>
<td>1.6%</td>
<td>0.3–3.6</td>
</tr>
<tr>
<td>postoperative red blood cell transfusion</td>
<td>13.9%</td>
<td>1.0–38.2</td>
</tr>
<tr>
<td>MACE</td>
<td>4.6%</td>
<td>2.5–7.3</td>
</tr>
</tbody>
</table>

BRIDGE - RCT: Cangrelor vs. Placebo *before* Cardiac Surgery

<table>
<thead>
<tr>
<th>Events</th>
<th>Cangrelor n=106</th>
<th>Placebo n=104</th>
<th>p-Wert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding (CABG-related)</td>
<td>11.8%</td>
<td>10.8%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ischemic events (death, MI, Stroke)</td>
<td>2.8%</td>
<td>4.0%</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

- Hospitalize patients presurgery for i.v infusion for 5 days?
- Not feasible for urgent surgery

Angiolillo et al., JAMA 2012
Perisurgery Pain Medication

- NSAIDs and Metamizol bind COX 1 and inhibit aspirin binding
- Concomitant application blocks the antiplatelet effect of aspirin
- Morphin inhibits clopidogrel metabolism

Hobl E-L et al. JACC 2014;63:630-5
Zusammenfassung – prohämostatische Therapie

• Thrombozytentransfusionen: keine Option bei ICB (Ausnahme bei OP-Pflichtigkeit?), mögliche Option perioperativ, keine Option bei Ticagrelor-Einnahme

• Desmopressin (DDAVP): verbessert die Plättchenfunktion nach Einnahme von Aspirin, nur teilweise nach dualer Plättchenhemmung, nicht nach Einnahme von Ticagrelor; unklares Risiko bei Stentpatienten

• Tranexamsäure: reduziert Blutungen und Transfusionen bei kardiochirurgischen Eingriffen, ohne erhöhtes Risiko für arterielle Thrombosen, unklares Risiko bei Stentpatienten

• rFVIIa (Novoseven): Ultima ratio bei Blutungen
What to do in case of acute bleeding in patients under anti-platelet therapy?
Treatment

1. **Airway, Breathing, Circulation**

2. Localize bleeding and close the vessel

3. Prohemostatic therapies

4. Restart anti-platelet drug in high risk patients after bleeding is controlled
Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial


<table>
<thead>
<tr>
<th>Type of antiplatelet therapy</th>
<th>n/N</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual antiplatelet therapy</td>
<td>35/189</td>
<td>1.62 (0.48-5.45)</td>
<td>0.78</td>
</tr>
<tr>
<td>Single antiplatelet therapy</td>
<td>154/189</td>
<td>1.80 (1.02-3.18)</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>120/190</td>
<td>1.97 (1.03-3.77)</td>
<td>0.94</td>
</tr>
<tr>
<td>UK</td>
<td>31/190</td>
<td>1.63 (0.42-6.31)</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>39/190</td>
<td>1.88 (0.61-5.74)</td>
<td></td>
</tr>
<tr>
<td>Haematoma volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma volume ≤7 mL</td>
<td>67/183</td>
<td>2.46 (1.02-5.94)</td>
<td>0.14</td>
</tr>
<tr>
<td>Haematoma volume &gt;7 to 30 mL</td>
<td>65/183</td>
<td>1.40 (0.58-3.39)</td>
<td></td>
</tr>
<tr>
<td>Haematoma volume &gt;30 mL</td>
<td>51/183</td>
<td>0.87 (0.27-2.76)</td>
<td></td>
</tr>
</tbody>
</table>

Unadjusted overall estimate 1.84 (1.10-3.08)
How to manage surgery?
Postoperative day (day 0 = day of surgery)

Platelet count ($\times 10^9$/L)

Greinacher A & Selleng K, BLOOD 2010

OP and day 3-5 highest risk for ACS
Thromboxane Synthesis
ASA Patients,
day 5 after Coronary Bypass (n=34)

Aspirin inhibition of cyclo-oxygenase

Modified from Sweeny JM et al. Nat Rev Cardiol 2009 doi:10.1038/nrcardio.2009.10
Morphine interferes with levels of active clopidogrel metabolites

Hobl E-L et al. JACC 2014;63:630-5