TRANSFUSION WITH COAGULATION PRODUCTS
FOR MANAGEMENT OF ANTICOAGULANT-
RELATED BLEEDING - BOTH OLD AND NEW

Sam Schulman, MD, PhD
Disclosures

• Honoraria from
  – Boehringer Ingelheim
  – Bayer
  – Daiichi
  – BMS

• Research grants from
  – Baxter
  – Octapharma
  – Boehringer-Ingelheim
Objectives

• To understand the risk-benefit of various regimens for reversal of warfarin
• To update on the possibilities to reverse glycosaminoglycans
• To discuss possibilities for reversal of the new, selective oral anticoagulants
Emergency situations on antithrombotic therapy

• Life-threatening bleeding
  – Intracranial bleeding
  – Spinal hematoma
  – Bleeding in the throat region
  – Massive G-I hemorrhage
  – Retroperitoneal hematoma with femoral nerve compression
  – Compartment syndrome (calf or forearm muscle)

• No bleeding but emergency surgery
  – E.g. dissecting aortic aneurysm
When to give platelet transfusions – and when not to

- If transfused, healthy platelets should not be inhibited by circulating platelet inhibitor
- For bleeding related to very short-acting inhibitor
  - Abciximab
  - Eptifibatide (Integrilin)
- For bleeding related to irreversibly bound inhibitor
PK of clopidogrel – ADP receptor inhibitor

- **Clopidogrel**
  - P450
  - T½: <1 h
  - Irreversible binding to platelet ADP-receptor

- **Active metabolite**
- **Carboxylic acid derivative**
  - T½: 7-8 h
Reversal of antiplatelet agents

- Clopidogrel: platelet dysfunction is not optimally reversed by DDAVP
- Platelet transfusion is effective
- Also for prasugrel
- But NOT for ticagrelor that binds reversibly ($T_{1/2} \ 9\ h$)
Vitamin K antagonist reversal

• Direct competition – Vitamin K$_1$ (phytonadion, phytomenadion)
• Replacement with the native $\gamma$-carboxylated factors
  – Plasma
  – Prothrombin complex concentrate
• By-pass – recombinant factor VIIa
# Options for normalization of hemostasis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin K</th>
<th>Plasma</th>
<th>PCC</th>
<th>rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of effect</td>
<td>12-24 h</td>
<td>2-6 h</td>
<td>15 min</td>
<td>10 min</td>
</tr>
<tr>
<td>Duration</td>
<td>Days</td>
<td>24 h</td>
<td>24 h</td>
<td>2-4 h</td>
</tr>
<tr>
<td>Volume</td>
<td>1 mL</td>
<td>2,000 mL</td>
<td>100 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>Dose</td>
<td>10 mg</td>
<td>20-30 mL/kg</td>
<td>20-30 U/kg</td>
<td>10-90 µg/kg</td>
</tr>
<tr>
<td>Effect on very high INR</td>
<td>Good</td>
<td>Moderate</td>
<td>Good</td>
<td>Questionable</td>
</tr>
<tr>
<td>Risk of thrombosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Vitamin K$_1$ pharmacokinetics

• T½ 1.5-3 h
• Full effect after 12-24 h
  – Compare with just holding warfarin
• Not effective in severe liver failure – no synthesis of coagulation factors
Vitamin K₁ administration

- **Intravenous** – caused anaphylactoid reactions*, mainly in old formulation with ricinomacrogol. Recommended in biliary obstruction.
- **Subcutaneous** – not recommended. Unpredictable, delayed response
- **Oral** – recommended in most situations

*Fiore LD et al. J Thromb Thrombolysis 2001: 3 per 100,000
Evidence

• RCT on IV (0.5 mg) vs PO (2.5 mg) for asymptomatic INR 6-10.
  – 6 h: 46% vs 0% in therapeutic range
  – 24 h: mean INR the same

• RCT on IV (0.5 mg) vs SC (0.5 mg) for asympt INR 6-10 (or 3 mg for >10)
  – 24 h: INR <5 in 95% vs 45%
  – Mean INR then 3.7 vs 5.4

De Zee et al. Arch Intern Med 2006
Nee R et al. Am J Cardiol 1999
## Vitamin K\textsubscript{1} indications (reversal)

<table>
<thead>
<tr>
<th>INR</th>
<th>Clinical condition</th>
<th>Dose</th>
<th>Alone or adjunct</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt;1.3)</td>
<td>Life-threating bleeding</td>
<td>10 mg i.v.</td>
<td>adjunct</td>
<td>1C</td>
</tr>
<tr>
<td>(&gt;1.3)</td>
<td>Serious bleeding</td>
<td>10 mg i.v.</td>
<td>adjunct</td>
<td>1C</td>
</tr>
<tr>
<td>(&gt;9)</td>
<td>No significant bleeding</td>
<td>2.5-5 mg p.o.</td>
<td>alone</td>
<td>2C</td>
</tr>
<tr>
<td>(\geq5-&lt;9)</td>
<td>No significant bleeding</td>
<td>1-5 mg p.o.</td>
<td>alone</td>
<td>2C</td>
</tr>
</tbody>
</table>

Ansell J et al. ACCP 7th-8th Conf. CHEST Suppl
Vit K for asympt INR 4.5-10

• 4 RCTs (3 reported TE and deaths)
• Follow-up 1-3 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vit K</th>
<th>Placebo</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>10/452</td>
<td>4/471</td>
<td>2.6</td>
</tr>
<tr>
<td>Thromboemb</td>
<td>5/423</td>
<td>4/441</td>
<td>1.3</td>
</tr>
<tr>
<td>Deaths</td>
<td>16/422</td>
<td>13/441</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Conclusion: Don’t routinely give vit K for asymptomatic high INR
Plasma versus PCC

- Volume overload, pulmonary edema
- Virus transmission possible
- Risk of TRALI
- Volume tolerated by almost all patients
- Virus inactivated
- TRALI not reported

The concentration of coagulation factors in PCC is 25 times higher than in FFP
• Complete reversal of vitamin K antagonists with plasma is not feasible when the INR is >5
• The volume required is too large.
• (Cohort study, 29 got PCC, 12 got plasma)
• … but can PCC generate thrombosis?

Evidence for PCC vs Plasma in ICH

- PCC (n=10) vs FFP (n=7)
  - Reaction Level Grade (RLG) progression
    - PCC: 0.2 grades
    - FFP: 1.9 grades (P<0.05)
- PCC (n=6) vs FFP (n=6, historical)
  - 15 min post-Rx INR: 1.32 vs 2.3
- PCC+FFP (n=5) vs FFP (n=8)
  - Time to corrected INR: 2.95 vs 8.9 h (P<0.01)
  - Signif fluid overload: 0 vs 5 (diuretics, CVP)

Boulis N. Neurosurg. 1999
Rapid effect of PCC (Beriplex® P/N)

Primary endpoint: Course of INR (mean +/- SD)

Mean INR 1.18 within 30 min
40 patients INR ≤1.3 (93%)
three patients INR 1.4 (7%)

Conversion of INR levels to percent for reversal with PCC or plasma

<table>
<thead>
<tr>
<th>Hemostatic condition</th>
<th>INR</th>
<th>Approx. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive anticoagulation</td>
<td>&gt;5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4.0-4.9</td>
<td>10</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>2.6-3.2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>2.2-2.5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1.9-2.1</td>
<td>25</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>1.7-1.8</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1.4-1.6</td>
<td>40</td>
</tr>
<tr>
<td>Normal hemostasis</td>
<td>1.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Dose of PCC/plasma = (Desired level – present level) X BW (kg)

Simplified dose calculation

Patient with major hemorrhage AND underlying thrombotic risk.

Full reversal not desirable, INR 1.5 acceptable

<table>
<thead>
<tr>
<th>INR on arrival</th>
<th>PCC U/kg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic – 2.5</td>
<td>20 U/kg</td>
</tr>
<tr>
<td>High – 4.0</td>
<td>30 U/kg</td>
</tr>
<tr>
<td>Extremely high &gt;10</td>
<td>40 U/kg</td>
</tr>
</tbody>
</table>

* Or plasma in mL/kg
Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study
Ravi Sarode, Truman J. Milling, Jr, Majed A. Refaai, Antoinette Mangione, Astrid Schneider, Billie L. Durn and Joshua N. Goldstein
Circulation. 2013;128:1234-1243

- ITT – 202 patients (PCC 98, FFP 104)
- Effective hemostasis: 72.4% vs 65.4%, non-inferior.
- INR ≤1.3 at 0.5 h post-infusion: 62.2% vs 9.6%, superior
- Safety: similar for SAEs, thromboembolism, deaths
- Fluid overload/similar cardiac event: 4.9% vs 12.8%
Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial

Joshua N Goldstein, Majed A Refaai, Truman J Milling Jr, Brandon Lewis, Robert Goldberg-Alberts, Bruce A Hug, Ravi Sarode
Lancet 2015; 385: 2077–87

• ITT – 168 patients (PCC 87, FFP 81)
• Effective hemostasis: 90% vs 75%, superior (difference 14.3%, 95% CI 2.8–25.8).
• INR ≤1.3 at 0.5 h post-infusion: 55% vs 10%, superior
• Thromboembolism: 7% vs 8%
• Fluid overload etc: 3% vs 13%
Standard vs individual dose PCC

Standard was 500 IU. Individual based on present & target INR & BW

N = 93
Design: RCT
open
Major bleed: 37
Surgery: 56
2 ischemic CVA

van Aart L et al. Thromb Res 2005
Reversal of heparin

- Protamine - mixture of arginine-rich, highly cationic, basic peptides, extracted from fish sperm cell nuclei
- Forms stable salt complex with heparin
- Only partial reversal of LMWH, danaparoid
- Given IV, max 50 mg/10 min
- Risk: histamin release, hypotension, bronchoconstriction. Platelet aggregation, consumption
Dosing of protamine

1 mg neutralizes 90 USP units of bovine UFH
or 115 USP units of porcine UFH

Example: Patient received 30,000 units UFH – starts bleeding

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Immediately</td>
<td>300 mg</td>
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<tr>
<td>After 1 h</td>
<td>150 mg</td>
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<tr>
<td>After 2 h</td>
<td>75 mg</td>
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</table>
Alternatives for LMWH reversal

- rFVIIa – case report: Overdose of enoxaparin → life-threatening intracerebellar hematoma.
- rFVIIa 100 mg/kg IV, 5 doses.
- →evacuation. Periop hemostasis very good.

Reversal of fondaparinux

- Plasma, PCC and protamine: 0 effect
- Hemodialysis reduces levels by 20%
- Heparinase I partly inactivates
- rFVIIa evaluated in healthy volunteers after fondaparinux 10 mg SC.
rFVIIa and fondaparinux

16 healthy volunteers
Same effect on ETP, APTT and PT
Similar study and
Results on idraparinux

Bijsterveld N et al. Circulation 2002;106:2550-4
Case report rFVIIa & fonda

- Orthopedic Sx, fondaparinux 2.5 mg
- Impaired renal function
- Severe wound bleeding after 1st dose → hemorrhagic shock. Got RCC. Still bleeding 39 h postop.
- Got rFVIIa 90 μg/kg and tranexamic acid
- Rapid cessation of bleeding

Patient with a-fib on dabigatran (RE-LY)

- CAD and aortic stenosis
- Elective CABG x 1 and bioprosthetic AVR
- Dabigatran held for 48 h preop
- Creatinine clearance 33 mL/min
- Hgb preop 97 g/L, got 2 U RCC preop
Open heart surgery April 8, 2008

<table>
<thead>
<tr>
<th>Time pm</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
<th>7</th>
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<tr>
<td>Hgb:</td>
<td>97</td>
<td>72</td>
<td>52</td>
<td>63</td>
<td>69</td>
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<td>86</td>
<td>84</td>
<td>90</td>
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<td>RCC</td>
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<tr>
<td>Plt:</td>
<td>131</td>
<td>109</td>
<td>86</td>
<td>86</td>
<td>99</td>
<td>94</td>
<td>131</td>
<td>105</td>
<td>127</td>
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<td>Plt-conc</td>
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<tr>
<td>INR:</td>
<td>1.4</td>
<td>2.2</td>
<td>2.0</td>
<td>1.3</td>
<td>1.1</td>
<td>1.1</td>
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<tr>
<td>APTT 60</td>
<td></td>
<td>94</td>
<td>76</td>
<td>55</td>
<td>51</td>
<td>45</td>
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<tr>
<td>TCT 2U &gt;150</td>
<td></td>
<td>&gt;150</td>
<td>&gt;150</td>
<td>119</td>
<td>129</td>
<td>126</td>
<td>128</td>
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<td>FFP</td>
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<td>Cryo</td>
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<tr>
<td>rFVIIa</td>
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<td>Tisseel</td>
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</table>
APCC vs rFVIIa in DTIs

Hemostasis in DTI therapy

- F XI $\rightarrow$ F XIa
- F IX $\rightarrow$ F IXa
- F VIII-VWF $\rightarrow$ F VIIIc
- F X $\rightarrow$ F Xa
- F V $\rightarrow$ F Va
- F VII $\rightarrow$ F VIIa
- F II $\rightarrow$ F IIa
- TF
- Fibrinogen $\rightarrow$ Fibrin
DTI and rFVIIa

F XI → F Xla

F IX → F IXa

F VIII-VWF → F VIIIc

F X → F Xa

F V → F Va

F II → F IIa

F VII → F VIIa

TF

Fibrinogen → Fibrin
DTI and APCC

F XI → F XIa

F IX → F IXa

F IX → F IXa

F VIII-VWF → F VIIIc

F X → F Xa

F V → F Va

F VII → F VIIa

F VII → F VIIa

F II → F IIa

F II → F IIa

Fibrinogen → Fibrin
Case report on dabi & FEIBA

- 67 y.o. male with AF, last dose dabi 7 h preop.
- Ablation Rx, UFH 5000 u, transseptal perforation, hypotension
- Pericardiocentesis: 4.5 L blood drained

Protamine 100 mg

FEIBA 3159 IU

Bleeding slows and stops

Dager W. Crit Care Med 2013;41:e42-6
4 Canadian cases

- All on dabigatran for a fib
- 81-85 years old
- All treated with aPCC (FEIBA) as the only coag product.

<table>
<thead>
<tr>
<th>Tamponade</th>
<th>Subdural</th>
<th>Intracranial</th>
<th>GI-bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Tamponade Image]</td>
<td>![Subdural Image]</td>
<td>![Intracranial Image]</td>
<td>![GI-bleed Image]</td>
</tr>
<tr>
<td>Crea 427</td>
<td>CrCl 45 mL/min</td>
<td>43</td>
<td>43 mL/min</td>
</tr>
<tr>
<td>FEIBA 100 u/kg</td>
<td>50</td>
<td>50</td>
<td>50 u/kg</td>
</tr>
</tbody>
</table>

Rivaroxaban and PCC

Antidote for dabigatran

- Monoclonal antibodies (Mab) generated in mice with dabigatran hapten
- Selection of best binding affinity profiles
- Then expressed in Fab-format
- Candidate clone 22 gave complete inhibition of dabigatran in human plasma or whole blood (specific Kd 34 pM)
- Approved by FDA (PraxBind®)
- Positive opinion at EMA

Idarucizumab was designed as a specific reversal agent for anticoagulant activity of dabigatran.

- Humanized Fab fragment
- Binding affinity ~350 x higher than dabigatran to thrombin
- No intrinsic procoagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion; immediate onset of action
- Short half-life

Idarucizumab shows immediate, complete, and sustained reversal of dabigatran anticoagulation in healthy volunteers.

'Normal upper reference limit' refers to (mean+2SD) of 86 predose measurements from a total of 51 subjects; dTT, dilute thrombin time.

Glund S et al. AHA 2013

No serious adverse events reported
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.
Primary endpoint in Group A: reversal of dabigatran anticoagulation with idarucizumab based on dTT and ECT

Idarucizumab levels are very low 12 hours after application

Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding; Pollack CV et al. N Engl J Med 2015;373-511-20

Additional information on clinical outcomes will be provided by the full study data set following recruitment of the planned 300 patients.
Decoy for reversal of FXa inhibitors (andexanet α)

- PRT4445/PRT064445 - a universal reversal agent for factor Xa inhibitors. Recombinant protein
- Similar to Xa but hemostatically inactive
- Binds to Xa inhibitors, prevents effect
- Escalating-dose safety and tolerability study, 32 volunteers – well tolerated.
- Phase II: reversal of apixaban, rivaroxaban, edoxaban
- Reverses fonda and enoxaparin well
- Phase III study in patients is recruiting

Two modifications introduced to human fXa

- Removal of the Gla-domain
- Mutation at the active site (Ser419Ala)
Annexa is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only.
Idarucizumab is in the most advanced stage of development of any NOAC reversal agent

Conclusions

- Clopidogrel or prasugrel-related bleeding – platelet transfusion
- Vitamin K acts slowly, use only in combination for major bleeding
- PCC is fast acting, seems safe and effective in emergency surgery and some bleedings.
- Dabigatran reversal – for now with APCC (or PCC). Soon idarucizumab.
- Rivaroxaban, apixaban – for now with PCC. In about 1 year andexanet-α